Estimating the Requirement for Chronic Kidney Disease Stage 5 (CKD5) Services in Romania

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'I, Andreea Steriu, confirm that the work presented in this thesis is my own.
Where information has been derived from other sources, I confirm that this has been indicated in the thesis.'

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In memory of Dan and Donna

To Michael and families

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Abstract

Background: Chronic kidney disease stage 5 (CKD5) with end-stage renal failure (ESRF) is not common but it is expensive to treat, despite advances in technology. Appropriate service provision requires good quality information on the population served and the services provided. In Romania this is in limited supply.

Aim: To estimate current and future service needs for CKD5 in Romania.

Methods: Desktop research, surveys of a sample of Romanian treatment centres, and mathematical modelling. The baseline renal replacement therapy (RRT) stock was calculated using the capture-recapture method (CRM). The reported % of cases with diabetic nephropathy was compared with the expected % based on population attributable risk (PAR%) and trends in disease precursors. The acceptance rate was estimated using the Impact Fraction method. Needs for numbers of treatment places were calculated from service activity and clinical parameters (stock, acceptance and mortality) in a spreadsheet model. Estimates were made under variant scenarios for two periods: calibration and validation (1997-2006) and projection (2007-2016).

Results: In Romania in 1997, the prevalence of chronic kidney disease (CKD) stages 1 to 5 was estimated at 1,222.5 per million population (pmp). There was a strong association between CKD5 and diabetes plus hypertension (OR =7.73 [95% CI: 0.99 to 60.38]). Increasing trends in age, diabetes and hypertension suggest an increasing incidence of CKD5; but a downward trend in smoking will offset this. Reported national RRT stock in Romania was 139 pmp in 1997 and 250 pmp in 2003. The CRM suggested that the Centre Questionnaire and EDTA data covered 71% of the total stock at baseline (2,995 patients). The % of CKD5 on RRT reported to have diabetic nephropathy was 10%, much less than the PAR%-based estimate of 30.5%. Acceptance and stock varied between the 14 centres from 11 to 85 pmp, and 112 to 222 pmp respectively. In the calibration period, two of the scenarios tried gave figures for 2006 of 238 and 251, close to the observed figure of 250. (Other scenarios gave figures from 238 to 721). Projecting the two chosen scenarios to 2016 gave 239 and 276 pmp. (Other scenarios gave up to 1,940 pmp.)

Conclusions: The information base for this modelling exercise was weak. However there appears to be under-provision of care for CKD5 in Romania, particularly for diabetic nephropathy.

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1 Introduction

1.1 Planning health care

One of the aims of any health care system is to improve efficiency by deriving increased benefits from scarce resources[1]. This challenge is particularly relevant to Romania, which has a lower GDP and devotes less of it to health care than most other European countries[2].

One priority area for planners of health care is the treatment of medical conditions that are costly to treat but have a substantial impact on morbidity and mortality, even though the absolute numbers of patients involved may be relatively low. This has to be balanced against care for other conditions that are more common but less damaging to health and/or less costly to manage.

1.2 Chronic kidney disease (CKD)

Chronic kidney disease does not rank high among causes of death[2] but it is of concern to managers and health services researchers because in most cases, without treatment, surviving with this chronic condition has a poor outcome. Moreover, treatment involves high technology and high costs of care, with an average of 12-15 hours treatment a week for a patient on haemodialysis[3, 4, 5] or for very limited numbers of patients, a transplant. Improving technology and an increasing pool or 'stock' of prevalent renal disease means greater demands on both providers of care and third party payers.

Health analysts have argued that in comparison with for example many cancers, treatment of end stage renal failure is effective in terms of avoiding years of life lost, and that in cost-benefit terms, more rational resource allocation decisions could be made [6, 7, 8]. Some of the relevant considerations have been set out by Cameron [6]:

What is the impact of CKD on the health status and the quality of life of a renal patient?

What is the impact on economic activity?

What is the impact on the patient's family?

What future can be expected for these patients as individuals and from the societal point of view?

1.3 The research question and approach

The research question is:

How might epidemiological and health care systems data be used to inform the planning of services for renal replacement therapy in Romania?

The approach is to:

i) review and collect relevant information on the epidemiology of renal disease and its risk factors;

ii) estimate future incidence and prevalence of renal disease and its risk factors;

iii) review and collect information on health care effectiveness, provision, policies and guidelines; and

iv) construct a health care system model to forecast future *health care needs* in the light of the future burden of renal disease, and to explore alternative service configurations.

1.4 Research outline: aim, specific objectives, methodology and methods, design and setting, outcomes

1.4.1 Aim

This research aim was to investigate the future requirement for treatment of CKD5 in Romania.

The intention was to provide evidence-based policy recommendations for the National RRT Programme under the political lead of the Ministry of Public Health and funded by the National Health Insurance Fund. The Romanian Society for Nephrology and Renal Registry were also stakeholders.

1.4.2 Specific objectives

The specific objectives of this research were:

1 to estimate the recent and current burden of CKD and its precursor conditions in Romania and on this basis to estimate the future burden;

2 to describe the baseline (1997) provision of services for CKD5 in Romania;

3 to measure observed clinical outcomes (survival) for a sample of patients with CKD5 undergoing RRT) in Romania;

4 to estimate RRT annual operational costs in a sample of Romanian units as a basis for a cost-effectiveness analysis (CEA);

5 to identify and describe relevant Romanian policies and clinical protocols, and to assess local RRT provision against these; and

6 to calibrate and validate an RRT treatment model for the Romanian national renal programme, and to make recommendations based on different model scenarios which may assist future service planning.

1.4.3 Methodology and methods

The methodology included:

i) a review of the relevant literature on the epidemiology of kidney disease (CKD) and its precursor conditions, on CKD5 and RRT, on clinical outcomes, on health economics (CEA or cost-effectiveness and including CUA or cost-utility) and on treatment modelling for CKD;

ii) collection of both quantitative and qualitative data, from both primary and secondary sources;

iii) supplementary analytical methods including capture-recapture and survival analysis to provide estimates of parameters for the treatment model; and

iv) a spreadsheet-based cohort model to estimate future needs for treatment for renal CKD5 in the light of changes in population, incidence of disease, survival and the availability of different treatment (RRT) modalities.

1.4.4 Data

Data were collected:

- for Romania as a whole and other countries, using secondary sources ;
- for Romania as whole using primary sources: a specially designed form (the Centre Questionnaire) and structured interviews with national key persons; and
- for different areas within Romania, from sampled RRT centres, using a specially designed form for individual patients, but also including cost data from the annual centre RRT programme and interviews with local key persons. These sources of data were mainly primary, but files and clinical notes were also consulted.

Data collection from primary and secondary sources and preliminary analyses for the empirical part were carried out during a 12 month period, from April 1998 to March 1999. Secondary sources of data were further used for follow-up by 2006 to 2008 for model validation purposes.

1.4.5 Settings

The setting for national level of information included nearly half of RRT adult centres in 1998; the CRM allowed for two-thirds of crude estimates to be considered as national CKD5 baseline in the treatment model. The settings for outcome, such as survival in newly accepted patients on dialysis and cost measurements were two teaching units and one district unit and these were at the basis of CEA.

1.4.6 Supplementary analyses

In order to validate the baseline stock estimate for the model and to supplement the information with a potentially better ascertained number of patients on RRT a capture-recapture method (CRM) was used with data from two quasi-independent data sources: the Centre Questionnaire and the European Dialysis and Transplantation questionnaire, both for 1997 data. Three historical cohorts from three centres were then used to calculate observed 1-, 2 and 3- year survival estimates. The Kaplan-Meier method was used and further, a Cox regression was used to identify possible variables which may influence survival of the Romanian CKD5-RRT patient.

1.4.7 The model

The model had a multi-centre historical cohort design. It was based on the following data from the sampled centres:

- age and gender profiles based on 38% of the CKD5 patient stock (source: Centre Questionnaire);
- probabilities of survival at 1- , 2- and 3 years for the Romanian CKD5-RRT patient. (Five- year survival probabilities were taken from the literature for validation purposes);
- differences in survival probabilities by modality of RRT (HD and CAPD);
- average cost per patient's treatment by modality in each of the three centres; and

- the cost per one year of life gained for the Romanian CKD5-RRT patient.

Estimated projections of precursor conditions were based on the population aged 15 years and over. The model was used to estimate the burden of renal disease in Romania in 2006 based on burden data for 1997, and a variety of scenarios for the other parameter values based on the evidence gathered during the study. The results were compared with Ministry of Health and National Health Insurance Fund data for 2006, and on this basis a reduced set of plausible parameter scenarios was chosen. This reduced set was then used to estimate the burden in 2016.

1.5 The structure of the thesis

Chapter 2 provides a review of the relevant literature. This covers epidemiology (definitions, natural history, indicators, mortality, morbidity including precursors and risk factors), the role of substitutive treatment and outcomes (survival and prognostic factors: complications, hospitalisation, and quality of life); and policy analyses (cost-of-illness and cost analyses, and model-based decision analyses). The chapter ends with a more detailed rationale for the study.

Chapter 3 introduces the original research and presents the results for objective 1. The estimates for the epidemiology of renal disease and diseases associated with progression to chronic renal insufficiency and ESRF in Romania are described. This chapter describes the epidemiological model: the methodology, methods and data sources and results. The main source is the national health survey of Romania (1997) and information from the Information and Statistics Centre of the MoH. Estimates for the leading causes of chronic kidney disease/chronic renal insufficiency and ESRF are placed in an international context, that of reported prevalence of primary renal diseases (PRD), hypertension (HT) and diabetes (DM). Strengths and weaknesses are discussed.

Chapter 4 presents the methodology, methods, data sources, data analyses and results on activity in the RRT network in Romania, showing the structure and functions of the various services involved, and national estimates for acceptance and stock rates. These results were used for calibrating the treatment model.

Chapter 5 presents the methodology used, methods, data sources and analyses with results from three sampled units for the following parameters: treatment activity based on acceptance and stock of patients; and clinical outcomes (survival).

Chapter 6 presents the methodology, methods and data source plus results on costs and cost-effectiveness analysis from the three sampled units.

Chapter 7 presents the information on treatment protocols and access to RRT for CKD5, based on interviews with national and local key persons and from secondary sources. Results for specific objective 5 are described.

Chapter 8 describes the treatment model, the type and methods used for its construction. Calibration and validation were carried out for a 10-year cycle from 1997 to 2006, using the 1997 baseline data. The model was then used to explore six scenarios in a second cycle from 2007 to 2016. Strengths and weaknesses are presented.

Chapter 9 presents a summary of the findings. The broader context of CKD is considered to highlight prevention strategies as well as the treatment requirements for CKD5. It consists of 3 main Sections: Discussion, Conclusions and Recommendations. The last section includes recommendations for further research.

2 The Literature

2.1 Introduction

The research question set out in Chapter 1 is concerned with estimating the requirement for renal replacement therapy in Romania. The subject matter for this literature review is based on a number of propositions:

- The requirement for renal replacement therapy is not necessarily related to historical patterns of resource allocation. Data on catchment populations and on the epidemiology of renal disease are important.
- Romanian data on the epidemiology of renal disease are sparse, but there are data from other Western societies which are relevant.
- Data on risk factors for renal disease can supplement and to some extent substitute for data on disease itself. Also planning involves estimating future requirements. The evolution of chronic renal insufficiency in an individual can take years, and so estimates of future requirements should be based on the distribution of 'upstream' risk factors and risk factor trends.
- Renal failure is a chronic condition. In the absence of a 'cure' or recovery, such as in the case of acute renal failure, it requires maintenance treatment (i.e. dialysis or a kidney transplant). Chronic functional failure develops in the context of chronic kidney disease. Thus planning the provision of services requires estimates and projections of prevalence. Projections of prevalence require projections of length of survival. Thus data on prognostic factors are needed.
- There is more than one way of managing renal failure, from the (ideally) one-off transplant to alternative modalities for long-term dialysis. Data on outcomes of treatment for the different modalities are needed.
- Services for chronic renal failure with CKD5 are costly and are in competition for resources with services for other conditions. As part of the process of considering options for provision, the costs and cost-effectiveness of different options should be considered.

- One of the main objectives of this study is to build a renal care system model for Romania. There are a number of these in the literature for other countries, and they will be reviewed.

For these reasons, the scope of the literature review is very wide. After a description of the search methods used, this chapter consists of:

- definitions of chronic kidney disease
- risk factors and precursor conditions
- disease progression and prognostic factors
- treatment
- outcomes
- the population burden of chronic kidney disease
- economic evaluation and cost-effectiveness studies; and
- decision support modelling for policy and planning.

Also in considering the extent to which existing services meet the needs, information is required on current levels of provision, and also on current policies and guidelines. These are topics for chapters 3 and 9.

2.2 Search methods

The following electronic libraries were searched: United States Renal Data System (http://www.usrds.org accessed in 1997; 2000; 2010 [9]; The Cochrane Library (2000 to 2009 for end-stage kidney disease reviews under the Cochrane Renal Group) at http//www.thecochranelibrary.com [10]; ANZDATA (New Zealand Renal Database) [11] ; this was accessed through the main European gateway to renal databases, the world-wide-web page of the European Renal Association- European Dialysis and Transplant Association, ERA-EDTA; www.ncchta.org (hypertension) [12]; www.uptodate.com [13]; www.dh.gov.uk (NSF Renal Services) [14]; BMC Nephrology (Open Access: 2000- 2007) [15] ; and most related journals through ADITUS (Athens library) for remote access of journals) [16].

MeSH key words used in searches relevant for each section of the literature review included:

- end stage renal disease OR failure (ESRD, ESRF for papers up to 2008; CKD from 2008) AND

- renal replacement therapy (RRT) AND :
- natural history, primary renal disease, hypertension, diabetes, obesity, mortality, survival, quality of life, utilities, complications, co-morbidity, computer modelling, competitive risk analysis, decision making, costs, cost analyses.

Each of these combinations of key words was searched (Appendix 1). This revealed a total of 788 papers. A further selection based on the abstracts reduced this to 250. Case reports and papers reporting case series with a very small number of patients, i.e. <30 per sample, were excluded (28 papers). Although some non-English-language research papers were considered, most were from the English and American literature.

The following journals, from a full list of journals provided in Appendix 1, were also hand-searched. After 2003 three of these were accessed electronically through ToC alerts:

1 American Journal of Kidney Diseases 1990 to 2011;
2 Journal of the American Society of Nephrology 1990 to 2011;
3 Kidney International 1990 to 2002; and
4 Nephrology Dialysis and Transplantation 1993 to 2012 (main access through personal subscription).

The initial literature search also yielded 33 relevant papers published before 1990, all related to haemodialysis. Publications have increased in number since the 1990s at least partly because of recent developments in dialysis technology, with a controversial literature on differences in effectiveness of different modalities: According to some studies, but not others, outcomes such as survival appear to be better with peritoneal dialysis than haemodialysis. A back search from references dating from 1997-2000 produced 7 relevant earlier papers, the earliest related to renal services dated 1968 [17]. Most papers published before the 1990s based their research on small samples (< 30 patients) and little comparative data and that is why they were excluded. Some Romanian grey literature was also consulted in the form of annual reports.

2.3 Definitions of chronic kidney disease

2.3.1 Clinical definitions

When kidneys are affected by a chronic disease their function is not impaired straight away. If one kidney is lost due to disease, surgery, etc, the other, if healthy, will fulfil the renal function at 100% efficiency. Chronic renal insufficiency, defined here as chronic

kidney disease (CKD) starts developing when less than 25% of the nephron population remains functional, regardless of whether the patient has one or two kidneys. Clinically it is described as mild when in an incipient phase (CKD1), and then moderate (CKD2 and CKD3a and 3b) progressing to severe (CKD4 and final CKD5). Although this study is concerned mainly with CKD5, the wider picture of chronic renal insufficiency and conditions leading to it is sketched in.

The definition and staging of CKD over the decades have been through a variety of formulations. The first dates from the mid 1970s (Cockroft-Gault) [18].

As a result there are several clinical terms for the condition or syndrome under study. Chronic kidney disease (CKD) has been the established terminology since 2009 [19], but, chronic renal failure (CRF), chronic renal insufficiency (CRI), end-stage renal disease (ESRD), end stage renal failure (ESRF) were used widely in the 1970s throughout the 1990s and even in the first decade of the new millennium. These latter terms were often used interchangeably by clinicians from Europe and North America [20, 21].

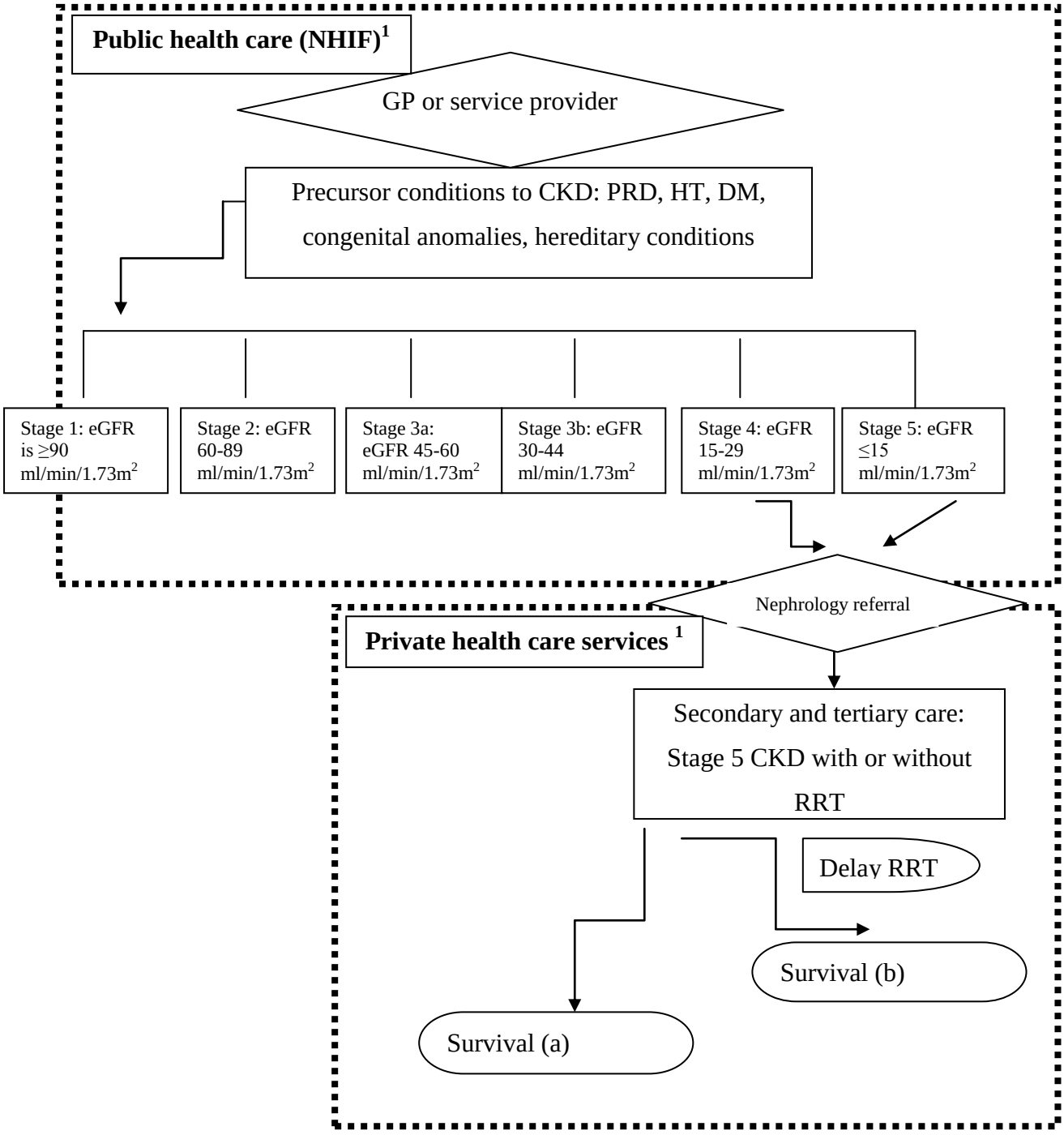
When kidney function is chronically affected, the spectrum of insufficiency of their functionality and clinical abnormalities can be characterised as falling into one of five stages. Middleton, quoting K/DOQI of the US National Kidney Foundation gives the staging in Table 2.1 [22] and Figure 2.1 adapted from Map of Medicine shows the flow diagram for assessment, investigation and management of CKD [23]:

Table 2.1: Staging of Chronic Kidney Disease and biological functionality

Stage	*Description*	*GFR (ml/min/1.73 m^2)*
1	Chronic kidney disease (normal GFR) (CKD1)	≥90
2	Chronic kidney disease with mild decrease in GFR (CKD2)	60-89
3	Chronic kidney disease with moderate decrease in GFR (CKD3a and 3b) [a]	30-59 (30-44 and 45-59)
4	Chronic kidney disease with severe decrease in GFR (CKD4)	15-29
5	Chronic kidney disease with function failure (CKD5)	<15

[a] some clinical differences were noticed in US patients with GFR at 45-59 ml/min/1.73m^2 compared with those at levels of 30-44 ml/min/1.73m^2

Fig 2.1 Chronic kidney disease – detection and management from primary care to tertiary care – adapted from Map of Medicine, UK ([1]Romania's health care system, 2011)



The five (or six) stages are commonly grouped as follows:

- early or mild to moderate chronic insufficiency *(stages 1-2):* functionally the kidneys are still being controlled by compensatory mechanisms, but on investigation, clinical and pathological abnormalities can be found such as an altered glomerular filtration rate (GFR). The patient usually seeks medical advice for general complaints such as

fatigue, headache etc. and renal insufficiency is discovered during routine biological check-up [24]; and

- late (stages 3-4 or 3a, 3b and 4) and end stage renal failure, ESRF (stage 5)*:* renal insufficiency is far enough advanced to be detected both clinically and pathologically. When CKD reaches stage 5, replacement therapy must be planned and access to a required RRT modality depends on many factors: age (but not solely), underlying precursor condition, co-morbidity, evolution and natural history. The extent of failure is usually defined by the levels of GFR. The great majority of epidemiological studies are at this "end" stage or CKD5, the "visible" tip of the larger iceberg of chronic kidney disease. Many patients also suffer from secondary complications from conditions leading to CKD before they enter RRT [25]; and the mild to moderate stages are an emerging area of research despite the fact that one classification dates since the mid-1970s [18].

Early formulae for determining clinical chronic renal insufficiency stages were based on measurable proxy variables: age, sex, weight and serum creatinine [18]. Later the Modified Diet in Renal Disease (MDRD) study established formulae which use between four and six variables (serum creatinine, serum urea nitrogen, serum albumin, age, sex and ethnicity) to predict the GFR and thus assign the stage of CKD [26].

The latest formula, after the MDRD (Modification of Diet in Renal Disease), is the CKD-EPI (Chronic Kidney Disease Collaboration). The two formulae, MDRD and CKD-EPI have been validated against each other and tried to standardise the criteria used in the definition of CKD. The authors (Earley et al) agree that neither the CKD-EPI nor the MDRD Study equation is optimal across all populations and GFR ranges. The authors conclude that using a single equation for reporting estimated GFR (marker of defining CKD stages) requires a tradeoff to optimize performance at either higher or lower GFR ranges. They further go on to say that "a general practice and public health perspective favors adopting the CKD-EPI equation in North America, Europe, and Australia and using it as a comparator for new equations in all locations". Moreover they specify that "whether the precision of creatinine-based equations can be substantially improved without adding other variables remains uncertain"[27]. This is despite the fact that other authors report in a meta-analysis that "the CKD-EPI equation classified fewer individuals as having CKD and more accurately categorized the risk for mortality and ESRD than did

the MDRD Study equation across a broad range of populations"[28]. The use of K/DOQI criteria were deemed valid for this study which considers CKD5 with renal insufficiency or failure under replacement therapy (Table 2.1).

2.3.2 Epidemiological definitions

Descriptive epidemiological studies aim to measure the frequency of occurrence of a disease in a defined population and time period, so as to provide an estimate of the associated population "burden"[29]. This requires a clear, explicit definition that can be used reliably by different investigators in different contexts.

The following selection of quotations helps to identify the relevant criteria:

- "Chronic renal failure (CRF) is the progressive decline in glomerular filtrate rate (GFR) that is often irreversible owing to progressive loss of functioning nephrons... The most reliable evidence of CRF is previously sustained increases in serum creatinine (Cr). An X-ray or renal ultrasonography with documentation of bilateral renal size less than 9 cm suggests CRF. In all other cases an elevated serum Cr is assumed to be due to acute renal failure (ARF)" [22; 25];
- "Renal injury of a more sustained nature which leads to progressive destruction of nephron mass;...proof of chronicity provided also by bilateral reduction of kidney size by plain X-ray, ultrasonograph exam, intravenous pyelography (BUN<100 mg/dl) or tomography; reliable, but not specific clinical and pathological proofs are: proteinuria, anaemia, hyperphosphatemia, hypocalcemia; specific signs in the urine sediment: broad casts, hematuria (deteriorated erythrocytes)" [30];
- "Chronic renal failure is defined as the irreversible, substantial, and usually long-standing loss of renal function causing ill-health, usually referred to as uraemia. End-stage renal failure is the degree of chronic renal failure that without renal replacement treatment would result in death. The severity of chronic renal failure can be classified by sequences and proportion of renal function lost, as mild (GFR =30-50 ml/min), moderate (GFR =10-29 ml/min), severe (GFR =<10 ml/min), and end -stage <5 ml/min)" [31].

In this research the focus was on CKD5 with its implication that kidneys have reached the final stage of an irreversible anatomical and functional deterioration, and the patient requires renal replacement therapy (RRT). The epidemiological definition of the CKD5

case chosen for this study was adapted from the K/DOQI definition of CKD staging and includes criteria as follows:

a patient who has:

- received continual renal replacement therapy for over 90 days, irrespective of the primary underlying renal disease
- *and* at least one abnormal biochemical result of:
  - serum creatinine: ≥ 9 mg/dl; and
  - glomerular filtrate rate (GFR)≤ 15 ml/min/ 1.73 m^2 (stage 5); and/or
  - bilaterally (or unilaterally if only one kidney), kidney sizes on a plain X-ray film or
  - ultrasonographic examination to be ≤ 9 cm;
- *and* at least one clinically diagnosed co-morbidity of:
  - anaemia
  - gastro-intestinal disorders,
  - neurological disorder,
  - cardio-vascular disorders,
  - raised blood pressure (≥ 140/90 mm Hg)

One reason for choosing these parameters and measurements was that these were used by the Romanian renal centres and Renal Registry in the definition of the condition at the time when the field work started in 1998.

2.4 Risk factors and precursor conditions

2.4.1 Introduction

Most of the patho-physiological factors that lead to renal damage are still not fully understood, and the relationship between uraemic syndrome and alteration of renal function varies from patient to patient. To summarise the literature, the emergence of chronic renal disease mostly depends on:

- primary renal diseases (PRD) such as lupus nephritis, analgesic nephropathy, ADPKD, chronic obstructive uropathy, etc [26]; [32, 33];
- muscle mass (large, muscular patients tolerate high level of azotemia) and dietary and nutritional status, which are also linked with obesity and diabetes [30] ;

- co-morbidity (co-existing conditions) where precursor conditions such as high blood pressure, diabetes and proteinuria with/without albuminuria, analgaesic use are key markers [10; 20; 32; 34];
- genetic determinants of diseases leading to nephropathy and renal insufficiency (e.g. type 1 diabetes which runs in families) [35, 36];
- personal and behavioural attributes, the main ones being smoking and obesity with signs of macro-vascular atherosclerosis; with implications for the micro-vascularisation (capillary) of organs playing an important role. Alcohol consumption has also been implicated, but the evidence for this is relatively weak.

Information on precursor conditions and risk factors in Romanian kidney disease patients is very limited. The focus here will be on the links between kidney disease (CKD5 especially, but also CKD) and: diabetes mellitus, hypertension, obesity and smoking.

2.4.2 Diabetes mellitus

Diabetes mellitus is a group of metabolic diseases characterised by hyperglycaemia resulting from defects in insulin secretion (type 1 diabetes mellitus or T1DM), insulin action (type 2 diabetes mellitus or T2DM; gestational diabetes mellitus (GDM); or both, (T2DM and/or other disorders). Chronic hyperglycaemia is associated with long-term organ damage, both vascular and tissue damage, dysfunction and failure. Kidneys are susceptible to such anatomical and physiological damage [37].

Evidence for this association is given by the high proportion of patients with diabetic nephropathy on renal replacement therapy, and also by the increasing acceptance of these patients on renal replacement therapy in countries around the world, where treatment capacity allows it. For example in the USA 36% of patients undergoing renal replacement therapy had diabetes mellitus as an underlying cause in 1991, increasing to 40% by 2000 [37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58]. Table 2.2 summarises findings from papers which illustrate the link between diabetes and end-stage renal failure from the world-wide literature [48; 59, 60, 61, 62, 63, 64, 65, 66];

Also in the USA, of those born in 2000 an estimated 33% of men and 38% of women may develop diabetes mellitus in their lifetime [67]. Until the end of 1990s the majority of cases of diabetes among children and adolescents (< 20 years) were immune-mediated type 1 diabetes. However, the prevalence of obesity has more than doubled in the past

two decades in the USA and this has led to an increase of type 2 diabetes in this age group [37; 56; 64]. The prevalence of diabetes is predicted to go on rising in the next two decades in all populations and so its impact as a leading cause for chronic kidney disease chronic renal insufficiency will be increasingly important when planning capacity for RRT [64].

In Canada, 29% of patients with CKD had diabetes mellitus as the primary cause in 1997, rising to 33% in 2001. One centre (Ontario) reported that 51% of its new patients entering renal replacement therapy had diabetic nephropathy [56]. After a follow-up for 8 years of 96% of the population from one Health Insurance Plan (7.4 million population of which 0.5 million had diabetes), those with diabetes were 12 times more likely to enter renal replacement therapy at the end of the 8 year observation period (an acceptance rate of 1,300 per million population for patients with diabetes compared to 110 for those without). The risk of developing chronic kidney disease and end-stage CKD5 was higher in those with diabetes, as high as ten times more. The Canadian study gives a RR (risk ratio) of 12 for incidence of end-stage renal failure in those exposed (with diabetes mellitus) over those unexposed [56].

Table 2.2: Diabetes linked to chronic kidney disease and CKD5

Diabetes	*Ref*	*year*	*Study*	*Sample*	*mean fu yrs*	*Exposed*	*baseline*	*End point/case definition*		*OR*	*95% CI*		*age*	*sex*	*smoking*	*obesity*	*alcohol*	*hypertension*	*social class*	*exercise*	Notes		
CKD	Fox C et al[49]	2004	Framingham offspr	2,585 US cohort	18.5	fasting glucose	> 126 mg/dl or med	GFR	m< 64 f<59 ml/min/1.73m2	2.38	1.45	3.92	*					*			GFR in lower %ile	< 59.25 in men	
	Domrongkitchaiporn S et al [50]	2005	Employees	3,499 Thai cohort	12	fasting glucose		GFR	< 60 ml/min/1.73m2	1.74	0.95	3.19	*	*	*	*		*			no adjustment for age and sex		
	Hallan SI et al [51]	2006	HUNT II	65,181 Norway		plasma glucose	>= 200mg/dl	GFR	< 60 ml/min/1.73m2	1.5	1.3	1.7	*								age only		
	New J et al [52]	2007	GP list	162,113 UK		GP recorded	not recorded	GFR	< 60 ml/min/1.73m2	6.14	5.7	6.5									unadjusted		
	Coresh et al [53]	2007	NHANES III	13,233		self-reported	absent	GFR	< 60 ml/min/1.73m2	1.54	1.28	1.80	*	*		*		*				1588/ 5072	10911/ 157041
	Shan54r et al [80]	2006	Wisconsin	4,926 US XS		plasma glucose	>= 200mg/dl or treatment	GFR	< 60 ml/min/1.73m2	3.58	2.63	4.86	*	*	*	*	*	*	E		adjusted for education		
	Chadban S et al55	2003	Australia AusDiab	11,247 XS		WHO criteria	absent	eGFR	< 60 ml/min/1.73m2	0.9	0.07	1.1	*	*				*					
CKD5	Lok CE [56]	2004	Ontario	7.5 million	8	DM	No-DM	Acceptance on RRT (CRF Stage 5)		12													
	Brancati F et al [57]	1996	MRFIT	US men 332,544	16	self-reported	absent	Dialysis or KD on death cert		9.9	7.4	11	*					*	*				
	Haroun et al [58]	2003	CLUE	23,534 US cohort	20	Treated	absent	Dialysis or KD on death cert		7.5	4.8	11.7	*		*								

In the UK Prospective Diabetes Study (UKPDS 64) over 5,000 patients with type 2 diabetes were studied. On the basis of observed and modelled data it was estimated that 25% of these patients will experience diabetic nephropathy within 10 years of diagnosis [44;60]. The proportion of those on renal replacement therapy with diabetes was 16% and 33% for white and Afro-Caribbean patients respectively, rising from 2% overall in 1976-78 to 19% in 1998 [61].

Studies of the association between diabetes mellitus and CKD (stages 3 to 5) have reported ORs from 1.5 to 6.1 while studies of the ORs for diabetes and CKD5 have reported values of between 7.5 and 12 (Table 2.2).

2.4.3 Hypertension

In the USA, 29% of patients undergoing renal replacement therapy had hypertension as an underlying cause in 1991, and this remains an important leading cause of chronic kidney disease and end-stage renal failure, second after diabetes, whether directly (essential hypertension) or indirectly through other cardiovascular involvement [65, 66]. Results from a number of studies are summarised in Table 2.3.

"At the end of the day we still don't have a clear understanding why even minor elevation of blood pressure increases the risk of end-stage renal disease. This fascinating problem with considerable public health implications will undoubtedly keep nephrologists busy in the years to come." [68] And although kidneys are target organs from raised blood pressure, there are no clear cut-off values of blood pressure at which organs such as the brain, heart or kidneys are more commonly affected. Nonetheless the recognised threshold for diagnosing essential hypertension (i.e. raised blood pressure with no other recognised cause) in adults is ≥140/90 mm Hg. These values are defined as "high normal". This stage is preceded by the optimal and normal stages and is followed by four stages (1-4) of raised BP of >140/90 mm Hg (JNC-VI: Joint National Committee on Prevention, Detection Evaluation and Treatment of high BP criteria for hypertension – Sixth Revision as quoted by USRDS) [9].

Essential hypertension shows a consistent but weaker association with chronic kidney disease and chronic renal failure than diabetes mellitus, with ORs ranging from 1.11 to 3.12 in different studies. The association between hypertension and end-stage renal failure may be slightly closer, with ORs from different studies ranging from 1.47 to 5.7 [49, 50, 51; 55, 56, 57 ; 58; 69, 70, 71, 72, 73, 74] (Table 2.3).

Individuals with hypertension are at even higher risk of chronic kidney disease if hypertension is associated with diabetes mellitus. This risk has not yet been robustly quantified [66; 73; 75] but in the UK around 6% of people with hypertension develop chronic kidney disease when in age group 50-74 year olds, but if the patient has both diabetes and hypertension, 17% go on to develop chronic kidney disease [70].

Table 2.3: Hypertension linked to chronic kidney disease and CKD5

Hyper-tension	*Ref*	*year*	*Study*	*Sample*	*mean fu yrs*	*Exposed*	*Baseline*	*End point/case definition*		*OR*	*95% CI*		*age*	*sex*	*smoking*	*Obesity*	*alcohol*	*diabetes*	*social class*	*exercise*	Notes	
CKD	Fox C et al [49]	2004	Framingham offspr.	2,585 US cohort	18.5	140/90 or medication	< 140	GFR	m< 64 f<59 ml/min/1.73m^2	1.57	1.17	2.12	*					*			GFR in lower %ile	< 59.25 in men
	Domrongkitchai porn S et al [50]	2005	Employees	3,499 Thai cohort	12	> 160	< 140		< 60 ml/min/1.73m^2	1.01	0.56	1.81	*	*	*	*		*			no adjustment for age and sex	
	Kurella M et al [69]	2005	ARIC	10,096 US cohort	9	waist > 88f 102m	waist <	eGFR	< 60 ml/min/1.73m2	1.99	1.69	2.35	*	*								
	Retnakaran R et al [70]	2006	UKPDS	2,392 UK diabetics	15	Ever	< 140	GFR	< 60 ml/min/1.73m2	1.11	1.06	1.16	*	*	*	*		*				
	Hallan SI et al [51]	2006	HUNT II	6,5181 Norway		140/90 or medication	< 140	GFR	< 60 ml/min/1.73m2	1.5	1.3	1.6	*									
	Chadban S et al [55]	2003	Australia AusDiab	11,247 XS		140/90 or medication	< 140	eGFR	< 60 ml/min/1.73m2	1.4	1.2	1.6	*	*				*				
	Shankar et al [54]	2006	Wisconsin	4,926 US XS		140/90 or medication	< 140	GFR	< 60 ml/min/1.73m2	3.12	2.46	3.96	*	*	*	*	*	*	e		adjusted for education	
	Coresh et al [53]	2007	NHANES III	13,233 XS		self-reported	< 140	GFR	< 60 ml/min/1.73m2	1.98	1.73	2.67	*	*		*		*				
CKD5	Klag M et al [71]	1996	MRFIT	US men 332,544	16	140/90	< 140/90	Dialysis or KD on death cert		3.10	2.3	4.3	*		*							
	Colhoun et al [72]	2001	WHO MSVDD	3558 type II DM	8.4	160	< 120	Dialysis or KD on death cert		1.0	0.7	1.4	*	*	*			*				
	Haroun et al [58]	2003	CLUE	23534 US cohort	20	160/100	< 120/80	Dialysis or KD on death cert		5.7	1.7	18.9	*		*							
						140/90	< 120/80	Dialysis or KD on death cert		3.2	1	10.4	*		*							
	Ishani et al [73]	2006	MRFIT	US men 12866	25	SBP	per 10mm	Dialysis or KD on death cert		1.31	1.19	1.43	*		*	*						
	Reynolds K et al [74]	2007	CNHS fu	China 158,365	8.3	140/90	< 140/90	Dialysis or KD on death cert		1.47	1.06	2.06	*	*	*	*	*	*		*		
	Reynolds K et al [74]	2007	CNHS fu	China 158,365	8.3	160/100 or medication	< 140/90	Dialysis or KD on death cert		2.60	1.89	3.57	*	*	*	*	*	*		*		

2.4.4 Obesity

The relationship between height and weight in adult populations is commonly measured using the Quetelet Index or BMI (Body Mass Index). Four categories are defined: underweight, normal weight, overweight and obesity. Overweight is defined as a BMI from 25 to 29.99 and obese as a BMI = 30 and above. (The obese category is further subcategorised from I to IV, with IV being morbid obesity.)

The effect of obesity as an independent risk factor for chronic kidney disease is inconsistent and depends on whether it is studied prior to renal damage or after it, and particularly if replacement therapy has been initiated. In most of the studies reviewed the ORs were between 1.2 and 1.7. The ORs for obesity and CKD5 were similar (Table 2.4). Increasingly chronic kidney disease in the setting of pre-diabetes "is considered as an additional complication of macro-vascular atherosclerosis, thus accelerating the progress towards end-stage renal failure" [73; 76, 77, 78].

Obesity is also a risk factor for diabetes and hypertension, and data on these risks are given in Table 2.4 and 2.5. The strength of the association was shown with the ORs for overweight (BMI <29.9) of 3.44 and for obesity (BMI ≥ 30) from 3.44 to 6.30. One study of overweight gave OR of 8.1 but this was unadjusted for other risk factors.

Table 2.4: Obesity linked to chronic kidney disease and CKD5.

Obesity	*Ref*	*year*	*Study*	*Sample*	*mean fu yrs*	*Exposed*	*baseline*	*End point/case definition*		*OR*	*95% CI*		*age*	*sex*	*smoking*	*alcohol*	*diabetes*	*hypertension*	*social class*	*exercise*	*Notes*		
CKD	Chen J et al.[75]	2003	PHS	11,104 US cohort		BMIb > 26.6	BMIb < 22.7	GFR	< 60 ml/min/1.73m^2	1.45	1.19	1.76											
	Fox C et al [49]	2004	Framingham offspr.		18.5	BMI baseline	per unit	GFR	m< 64 f<59 ml/min/1.73m^2	1.23	1.06	1.41	*	*	*		*	*			GFR in lower %ile	< 59.25 men	< 64.25 women
	Gelber R et al [76]	2005	PHS	11,104 US men	14	BMIb > 26.6	BMIb < 22.7	GFR	< 60 ml/min/1.73m^2	1.45	1.19	1.76	*	*	*	?	?						
	Kurella M et al [69]	2005	ARIC	10,096 US cohort	9	waist > 88f 102m	waist <	eGFR	< 60 ml/min/1.73m^2	1.18	1	1.4	*	*									
	Domrongkitchaiporn S et al [50]	2005	Employees	3,499 Thai cohort	12	BMI > 25	BMI <= 25		< 60 ml/min/1.73m^2	1.68	1.02	2.77	*	*	*		*	*					
	Ejerblad E et al [77]	2006	Population register	1,924 Sweden CC		BMI > 25 at 20	BMI <= 25	Serum creat	> 3.4 mg/dl (M) or 2.8 (F)	3.1	2.1	4.8	*		*	*			e		women: 3.0 (1.4-6.1)		
	Shankar et al [54]	2006	Wisconsin	4,926 US XS		BMI > 25	BMI <= 25	GFR	< 60 ml/min/1.73m	1.2	0.83	1.73	*	*	*	*	*	*	e		adj for education		
CKD5	Stengel et al [78]	2003	NHANES II	9082 US cohort	12-16 y	BMI > 35	BMI < 25	Dialysis or KD on death cert		1.3	0.6	2.9	*	*	*		*	*					
	Ishani et al [73]	2006	MRFIT	US men 12866	25	per 5 units	BMI	Dialysis or KD on death cert		1.17	0.95	1.44	*		*			*					
	Hsu C et al.[7]	2006	Kaiser	320,252	26.1	BMI 30-34	BMI < 25	Dialysis or KD on death cert		2.98	2.54	3.49	*	*	*		*	*					

Table 2.5: Obesity linked to diabetes and hypertension.

Obesity	*Ref*	*year*	*Study*	*Sample*	*mean fu yrs*	*Exposed*	*baseline*	*End point/case definition*	*OR*	*95% CI*	*age*	*sex*	*smoking*	*alcohol*	*diabetes*	*hyperte nsion*	*social class*	*exercise*		*Notes*
Diabetes	Colditz et al 1995[79]	1995	nurses health	114,281 US cohort	14	BMI 25-26.9	BMI < 22	self-reported diabetes ++	8.1	6.2	10.5	*								
	Mokdad A et al [89]	2003	telephone survey	195,005		BMI 30-39	BMI < 25	self-reported diabetes	3.44	3.17	3.74	*	*	*						adjustment for age, sex, education, smoking & ethnicity
	Wannameth ee G et al [80]	1998	BRHS cohort study	7,176	20	BMI 27.5-29.9	BMI < 25	GP reports	3.64	2.74	4.83	*	*	*			*	*	*	adjusted for age, social class, smoking, alcohol, phys activity etc
						BMI 30+			6.30	4.67	8.51	*	*	*				*	*	
Hyper-tension	Mokdad A et al [89]	2003	telephone survey	195,005 XS		BMI 30-39	BMI < 25	self-reported hypertension	3.50	3.31	3.70	*	*	*		*			*	adjustment for age, sex, education, smoking & ethnicity
	John U et al 2006[81]	2006	national survey	6,903 Germany XS		BMI 30+	BMI < 25	SBP, DBP mild >140 or > 90	2.80	2.30	3.40	*	*			*			*	adj: age, sex, CHD, alcohol, smoking, exercise etc
								treated hypertension	8.60	6.70	11.1	*	*	*		*			*	adj: age, sex, CHD, alcohol, smoking, exercise etc

2.4.5 Smoking

Smoking has been associated with increased risk of chronic kidney disease in two longitudinal studies in the USA, a case series in the UK and a case-control study in Sweden (Table 2.6). All these studies were representative of the adult populations in their countries. ORs for smoking and end-stage renal failure ranged from 1.84 to 2.60. They, and others, all concluded that smoking affects blood vessels via arteriosclerosis and may act as an independent risk factor for chronic kidney disease [49, 50;54; 70; 77].

In one systematic review of 17 studies it was found that smoking remained a risk factor for the development of chronic renal disease in men (RR= 2.4, 95%CI from 1.2 to 4.5), in those smoking over 20 cigarettes a day (OR= 1.51, 95%CI from 1.06 to 2.15) and in those smoking for more than 40 years (OR= 1.45, 95%CI from 1.00 to 2.09). The review could not provided a pooled estimated relative risk due to heterogeneity of studies [82].

The ORs for chronic renal failure associated with smoking were reported as from 1.34 to 2.1 [54; 70; 77]. However a Thai study found no effect [50]. The systematic review by Jones-Burton et al found values from 1.45 to 2.4 [82].

Smoking is also a risk factor for diabetes (OR =1.44) and possibly for hypertension [83]. Data on these risks are given in Table 2.7. However there is mounting evidence that any links between smoking and hypertension are, in fact, the product of confounding between smoking and obesity, possibly via another factor, such as a sedentary lifestyle. Thus for people with a BMI in the normal range there is very little evidence that smoking carries an excess risk of hypertension [81; 84, 85, 86].

Table 2.6: Smoking linked to chronic kidney disease and CKD5

Smoking	*Ref*	*year*	*Study*	*Sample*	*mean fu yrs*	*Exposed*	*baseline*	*End point/case definition*		*OR*	*95% CI*		*age*	*sex*	*smoking*	*obesity*	*alcohol*	*diabetes*	*hypertension*	*social class*	*exercise*	*Notes*		
CKD	Fox C et al [49]	2004	Framingham offspr.	2,585 US cohort	18.5	smokers at baseline	non-smokers	GFR	m< 64 f<59 ml/min/1.73m^2	1.42	1.06	1.91	*					*	*			GFR in lower %ile	< 59.25 in men	<64.25 in women
	Domrongkitchaiporn S et al [50]	2005	Employees	3,499 Thai cohort	12	Smokers	non-smokers		< 60 ml/min/1.73m^2	1	0.7	1.45				*		*	*			no adjustment for age and sex		
	Retnakaran R et al [70]	2006	UKPDS	2,392 UK diabetics	15	Ever	non-smokers	GFR	< 60 ml/min/1.73m^2	1.34	1.28	1.4	*	*		*		*	*					
	Ejerblad E et al 77	2004	Population register	1,924 Sweden CC		> 20/day	non-smokers	Serum creat	> 3.4 mg/dl (M) or 2.8 (F)	1.51	1.06	2.15	*	*			*			e				
	Shankar et al [54]	2006	Wisconsin	4,926 US XS		smokers	non-smokers	GFR	< 60 ml/min/1.73m^2	2.1	1.57	2.81	*	*		*	*	*	*	e		adjusted for education		
CKD5	Colhoun et al [72]	2001	WHO MSVDD	2,559 type II DM	8.4	smokers	non-smokers	Dialysis or KD on death cert		1.2	0.8	1.8	*	*				*	*			RRs		
	Stengel et al 78	2003	NHANES II	9,082 US cohort	12-16 y	<20/day	non-smokers	Dialysis or KD on death cert		1..4	0.7	2.7	*	*		*		*	*					
						>=20/day	non-smokers	Dialysis or KD on death cert		2.3	1.2	4.3	*	*		*		*	*					
	Ishani et al [73]	2006	MRFIT	US men 12,866	25	smokers	non-smokers	Dialysis or KD on death cert		1.84	1.35	2.51	*			*			*					
	Haroun et al [58]	2003	CLUE	23,534 cohort	20	smokers	non-smokers	Dialysis or KD on death cert		2.6	1.8	3.7	*					*						

Table 2.7: Smoking linked to diabetes and hypertension.

Smoking	*Ref*	*year*	*Study*	*Sample*	*mean fu yrs*	*Exposed*	*baseline*	*End point/case definition*	*OR*	*95% CI*		*age*	*sex*	*obesity*	*alcohol*	*diabetes*	*hypertension*	*social class*	*exercise*	*Notes*
Diabetes	Willi C et al [83]	2007	25 studies	1,2 million		smokers	non-smokers	Diabetes	1.44	1.31	1.58	*		*						All but 3 studies adjusted for age and BMI; 14 biologically screened, 10 questionnaire, 1 med exam
Hyper-tension	Fogari R et al [84]	1996	Employees	7,109 Italy XS		smokers	non-smokers	SBP difference in mean	NS			*		*						No difference in BP between smokers/non smokers with normal weight; for obese smokers had higher bp in 18-30 only
	Primatesta et al [85]	*2001*	HSE	*33,860 England XS*		*smokers*	*non-smokers*	*SBP linear*	*NS*			*		*	*			*		"any independent chronic effect of smoking on BP is small" " increase in BP with smoking only seen in age 45+ overweight men, and also linked to alcohol consumption"
	Halimi JM et al [86]	2002	Population	12,417 France XS		current	never	SBP	NS			*		*	*					1.31 for unadjusted by BMI
	John U et al [81]	2006	national survey	6,903 Germany XS				SBP: mild >140 and DBP: > 90 or treatment (treated HT)	1.1	0.9	1.4	*	*	*	*	MI			*	Smoking hypertension paradox may be explained by obesity and overweight. No trend in Ht with smoking among those with normal weight

2.5 Disease progression and prognostic factors

Apart from the few who are given a transplant, most people with end stage renal failure will continue on dialysis until they die. Thus the requirement for dialysis depends on length of survival as well as disease incidence, and any changes over time in the factors that affect survival will need to taken into account when estimating the capacity required to meet future needs. Prognostic factors also affect policies relating to patient selection by treatment centres [5; 26; 87, 88] and methods of case-mix adjustment in observational studies of outcome, such as comparisons between treatment modalities or centres. However according to Williams and Mallick [89]:

> "The natural history of renal disease in which there is a primary structural, metabolic, or immunological abnormality is … complex since there are few occasions when progression due to the underlying disease can be differentiated from progression due to adaptive factors".

Among adaptive factors is the secondary hypertension triggered by sub-normal functioning of the kidneys. Secondary hypertension is a separate topic and is not considered further here. Nonetheless a number of patients' attributes have been associated with progression of chronic kidney disease and reduced survival on RRT. Age, primary renal disease and co-morbidity mix have received most attention [60; 66; 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102,] For example:

- '...age at entry on RRT, type of RRT, hypertension and diabetes increase the risk of death...' [60;66; 91, 92];
- '.age, sex and race are useful predictors of mortality...initial diagnoses at time of first dialysis, such as: diabetes, hypertension, glomerulonephritis, polycystic kidney and collagen diseases (diagnostic aggregations) are reasonably predictive, but there is likely to be substantial unmeasured severity within these diagnostic cells...' [92];
- '...age, race, cause of renal failure, nutritional impairment, and, the presence of cardiovascular disease are the main predictive mortality risk factors in patients receiving dialysis...treatment time was found to be inversely related to mortality' [94,95,96,97];
- '...serum creatinine concentration, urea reduction ratio (URR), albumin, anion gap...are the most important associates of death risk...' [100, 101], and cholesterol levels...'[102];

- '...risk group [classification of patients under RRT in: low, medium, high risk, according to primary renal disease and co-morbidities] was the strongest predictor of mortality [93]...diabetes and myeloma were also associated with a significantly high risk of death...each additional year in age at the commencement of RRT increased the risk of death by 3.1%...[102];

Age profiles in patients undergoing renal replacement therapy have changed in the past 30 years. One study shows that in the UK 1% were aged 65 years or older in 1976-78. By 1998 this proportion had risen to 47% [60].

According to the National Institute for Clinical Excellence (NICE) in England and the National Collaborating Centre for Chronic Conditions: 'the evidence on the effects of obesity on the risk of progression of renal disease is un-convincing' [103], [104]. However there is evidence from several large studies that obesity actually has a protective effect among people who are on haemodialysis:

- ' …. the effect of overweight (BMI: 25–30) or obesity (BMI: >30) in patients with chronic kidney disease (CKD) undergoing maintenance haemodialysis (MHD) is paradoxically in the opposite direction; i.e., a high BMI is associated with improved survival or, so called "reverse epidemiology"… [105, 106].

and there is:

- : '… no evidence supporting the intuition that smaller patients require proportionately lower dialysis dose than larger patients [BMI related], that is once a patient is under HD…' [103].

Type 1 and type 2 diabetes mellitus progress differently. After diagnosis of type 1 diabetes, the incidence of chronic kidney disease rises from 2.2% at 20 years and 7.8% at 30 years. Although overall survival has improved markedly (by 50%) in cases diagnosed in the 1970s compared with those diagnosed in the 1960s, type 1 diabetes has shown a steady and relatively slow natural progression towards end-stage renal failure [40; 45, 46, 47].

Because type 2 diabetes has only been increasing since the late 1990s, survival studies have yet to demonstrate an impact on need for renal replacement therapy.

One Austrian study, with small samples of type 1 and type 2 diabetes, suggested that survival in treated type 2 diabetes patients was worse than for type 1: 80% vs. 100% at 1 year but 82% vs. 29% at 5 years. The difference is partially explained by the difference in age; the type 2 diabetes

patients were much older. However, apart from age, the study observed that the prevalence of cardio-vascular morbidity and peripheral vascular disease was significantly higher in the type 2 diabetes patients than non-diabetic patients. Most importantly, an increase in the proportion of type 2 diabetes patients entering treatment was noted and also because of co-morbidity and complications, these patients were less likely to receive a transplant [64].

Finally, '…early referral to nephrology services has been shown to be a prognostic factor e.g. in the UK [107].

Despite the importance of prognostic factors, research in this area has many challenges. Among the recommendations are: better definition of primary outcomes; and improvements in methodological standards and on reporting standards by using guidelines[108].

To summarise, the prognostic factors for end-stage renal failure that will be considered in here are: primary renal disease, diabetes and hypertension. Age, sex, obesity and smoking are considered in discussion as likely to be influential in future. These variables should be considered in future epidemiological models as prognostic factors for outcome as well as risk factors for disease [9; 48;58;60].

2.6 Treatment

Once a patient has developed CKD with renal insufficiency the course of the disease can be affected by:

> "…conservative therapy (non-dialytic, non-transplant therapy), which, if instituted early, could control symptoms, minimise complications, prevent long term sequelae and slow the progression of renal insufficiency…" [30].

Modification of diet and compliance with modified dietary regimes are of great importance, as they can delay the need for renal replacement therapy [26;32;89]. However, if a primary renal disease (or a systemic disease) leads to renal insufficiency that in time becomes chronic and progresses into end stage renal failure. Eventually, without renal replacement therapy the patient will die [89; 97; 109].

The possible modalities for of renal replacement therapy in end-stage renal failure include:

- in-centre haemodialysis (HD), whether staff dependent or self-care;

- home haemodialysis, where the home environment is adapted to use a HD station, a common approach in the USA;
- home continuous ambulatory peritoneal dialysis (CAPD); and
- home continuous cycling peritoneal dialysis (CCPD).

Patients for whom CAPD is favoured over the in-centre HD modality in end-stage renal failure include: patients with severe cardio-vascular disease; patients with difficult vascular access (e.g. diabetics); patients who desire greater freedom to travel; and patients who wish to perform home dialysis, but do not have a suitable partner or resources to be assisted. Home HD is frequently used in the USA [9], whereas in Europe, hospital or in-centre HD and CAPD are the main modalities [110; 111; 112].

If a patient suffers from acute fluid overload, which may happen between haemodialysis sessions, then dialysis is supplemented with ultra-filtration which removes the excess fluid. Special HD stations are used, called haemo-dia-filtration (HDF) stations. The predilution variant of HDF is gaining better quality of treatment status according to most recent studies, with achievement of better creatinine clearance during HD sessions of same length of time and frequency [112]. HD has evolved in a combination of methods which are tailored to suit the patients' needs. Outcomes are promising in terms of survival and quality of life although results come from small cohorts of patients.

Transplantation is a third modality, with first and second haemodialysis and peritoneal dialysis. Usually one kidney is placed in the lower abdomen of the recipient. Transplantation can be performed with a kidney from a living related donor or someone who has a very good HLA (genetic) match or with a cadaver donated kidney, again matched by HLA properties. The A stands for antigen and the closer the match between donor and recipient, the lower the level of antibodies which may reject the transplanted organ[113].

The complexity of cases can results in patients moving from one modality to another [32]. Patient preferences and clinical decisions about type of therapy have been much debated over the years, and vary from country to country [93]. In the mid 1990s Canadians reported better survival on PD, while a study from the USA reported better survival on HD [113]. However, Kjellstrand and others have taken the view that:

"...the influence of dialysis technology on mortality is meaningless, and most of the differences can be explained by different patient populations and transplant rates..." [114, 115].

and

"case-mix differences may underlie these paradoxical results and registry data should be careful interpreted.....There is no convincing proof that true differences in mortality rates exist between haemodialysis and peritoneal dialysis....The modalities should be viewed as complementary, and attention to detail in patient care should be emphasised for both"[114].

Two later reports in 2003 showed that different risks of mortality between peritoneal dialysis and haemodialysis were obtained when the data were analysed using different statistical models. The differences found in the estimated hazard ratio (HR) between the modalities were not related to the therapies themselves, but were instead determined by the variables included in the analysis [116], [117]:

"…there was no randomness; timeframe and sample size played a role…";

One point on which the published literature is agreed is that survival and quality of life of transplant patients is better than patients undergoing dialysis at all ages. In 2009 a study from a large cohort of patients (25,287) in Australia and New Zealand suggested that treatment with peritoneal dialysis may be advantageous initially, but may be associated with higher mortality after 12 months [118, 119].

2.7 Supply

Increasingly, research supports the hypothesis that factors related to the supply and provision of renal replacement therapy such as referral time or access to a nephrologist, waiting time and/or inclusion on a transplantation list, and formal multi-disciplinary clinic (MDC) based care, can influence survival and some clinical guidance includes strategies of delaying the onset of RRT [60; 87; 107; 109; 120, 121, 122, 123, 124]. For example:

- '…referral to nephrologist as "time in nephrological care" in the predialysis phase; age and, also being a male – the patient is more affected and overall prognosis is poorer…' [60; ; 87; 107;109;
- '...NICE recommends the use of ACE-I when there is hypertension to maintain BP below 140 (systolic) and 90(diastolic); NICE divides stage 3 of CKD in 3a and 3b and recommend testing for bone disease and anaemia in stage 3b (eGFR 30 to 44), as well as stage 4 and 5' [120]. This

suggests some rationing during the progression of disease, but monitoring of kidney damage through clinically monitoring proteinuria and blood pressure have been defined good practice by 2012.

The problem is that:

"....there is no universally agreed-upon index to summarise the severity of illness...and which would have value in adjusting the case mix..." It has been suggested that "the Khan, Davies and the Charlson indices will adjust to the same extent for the potential confounding effect of comorbidity in studies with health status as an outcome. Separate co-morbidity diagnoses will adjust best for co-morbidity and treatment referral" [5; 91; 97]; and it has been identified that:

"...macroeconomic and renal service factors are more often associated with RRT incidence rates (or acceptance on RRT) than measured demographic or general population health status factors in this 46 country analysis..." [121]; and that

"...The global burden of ESKD (end-stage kidney disease) or CKD5 is concealed behind statistics which reflect only the number of people treated, not those who die of kidney failure or cardiovascular complication…" [115]; thus the issue of equity is also raised when treatment supply is addressed.

It is clear from clinical practice and the literature that any form of RRT may improve survival, depending on a variety of circumstances and factors. However, by mid-2000s none of renal replacement therapy, let alone the role of population estimated glomerulo-filtrate rate (eGFR) screening in reducing the incidence of stage 5 of the condition, has ever been subjected to a large phase III clinical trial. For example, haemodiafiltration as new procedure (new in comparison with the 'simple' haemodialysis itself) is the only one to have undergone such a trial after a decade of case series studies [112]. In the absence of a definitive proven method of risk adjustment it is difficult to determine which treatment modality is most effective for which patient groups or what benchmarking can be used when variations in the timing of dialysis initiation may explain some variations in RRT incidence [123]. This is despite the fact that one country seems to have found an optimum RRT combination for good outcomes and quality of life associated with affordability in supply, yet this country also addresses an equitable supply [112;124].

Romania has changed its levels of RRT supply from 1990 to 2004 with little documented analysis of association with treatment outcomes or equity [122].

2.6.1 Specific technologies

There is a growing health technology assessment literature which tends to be based on intermediate, 'proxy' or surrogate outcomes such as haemoglobin or haematocrit levels, dialysis adequacy, lipid profile, and adverse symptoms during a dialysis session. Most of these could affect downstream outcomes such as survival and quality of life. One of the most comprehensive groups of systematic reviews was published by MacLeod [125]; other papers have also been reviewed, particularly in the light of the quality of evaluations of interventions [120]. The UK systematic review gave recommendations for the English National Service Framework (NSF) for Renal Services in 2002. Some of the factors found to affect outcomes include [14]:

Synthetic vs modified cellulose membranes: in a UK led meta-analysis, the use of synthetic membranes significantly ameliorated HD treatment; Romanian data show that between 1996 and 2003 the use of synthetic membranes rose from 5% to 63% [122];

Bicarbonate-buffered vs acetate-buffered dialysate in HD for CKD5; Romanian data show that between 1991 and 2003 the use of bicarbonate-buffered dialysate rose from 0% to 63% [122]; and

Y-set/ modified Y-set versus standard spike as CAPD delivery system for patients with end-stage renal failure; Romanian data show that all patients since CAPD was introduced in 1996 are treated on Y-sets or modified Y-sets [41; 122].

2.7 Need

Need for a treatment has many definitions. Spassof quotes Stevens and Raftery in the way they place "the conceptualization of need in a broader context and based on Bradshaw's approaches" to define need:

- Normative need: "objectively" measured by professionals;
- Felt need: equivalent of want or expectation; "subjective";
- Expressed need: in seeking care; this need is related to demand or requirement; the individual would utilise the service at a given cost;

- Comparative need: a lower use of services than enjoyed by some comparable population.

In public health, the generic term 'need' is used in relation to both the illnesses or health shortfall that people experience (need for 'health') and for the treatment appropriate to their illness (need for 'health care'). A key role of public health practitioners is to assess both the health and the health care needs of a given population. Such health needs assessments can at best ensure that health-care provision, RRT for CKD5 in this case, is evidence based. The findings of health needs assessments should then guide allocation of resources, with the main aim of improving health care efficiency and reducing population health inequalities.

The definitions of need most useful for this research are the expressed need or requirement for RRT, and comparative need, which relates to evidence-based provision, equity and thus addresses health inequalities. The affordability of RRT is a concern in most countries which have cash limited health care systems. As a result an evidence-based needs assessment (EBM), a cost-effectiveness analysis (CEA) and the development of a valid and reliable treatment model could be the starting point for evidence-based provision of care for CKD in Romania.

2.8 Outcomes

2.8.1 Survival and case fatality under RRT

Since end-stage renal disease is fatal without treatment which conserves the renal function or RRT, survival is:

> "...the ultimate outcome measure of the success of RRT and may increasingly be used as a quality assurance tool to compare the performance of centres providing such treatment and to determine funding..." [99].

The 1997 USRDS and later Annual Reports and EDTA reports compare 1-, 2-, and 5-year survival rates for various incident cohorts of dialysis patients. The USRDS for 1993 reported an all-age survival rate of 75.3%, (i.e. ≈ 25 deaths per 100 renal patients on RRT), increasing to 80-82% for 1999 [9].This is quite low when compared with some cancers, such as breast cancer, which have a 5-year survival of 80% [82]. However, the USA reports high met need for RRT and non-selective acceptance on to RRT may result in a complex case mix in terms of co-morbidity, advanced age, etc. [9]. The 1-year and 5-year estimates for 1997 for the European Registry were 82% and 47% slightly better than in 1992 [122; 126] .

Most of the improvement in years of life under treatment occurs in the early years of therapy, apart from the first 3 to 6 months when survival is relatively poor. Japan reports a quarter of their patients surviving at 10 years or more [112].Occasionally patients survive for longer than 20 years [101].

Since the mid 1990s, severity of case mix has been estimated by measuring case fatality in the first 90 days on RRT. It has been reported that between 1.8 and 11.4% of patients die during this period; among the causes, cardiac and social causes are commonly quoted in the literature. The extent of late referral, as a predictor of early death on treatment, may also vary very widely across countries, depending on the definition of 'late'. This is a possible explanation for the variation in early case fatality on RRT [103].

However, researchers have agreed to exclude these deaths from the counts and indicators measuring the annual national renal replacement therapy acceptance and stock, as well as when measuring survival, in order to provide meaningful information on rates for chronic replacement therapy. The 90- day mortality is reported as significant if more than 10% of those who enter RRT die within the 90- day period [107].

Survival for 5 years was shown to be better for an American 1990 cohort than for the 1985 cohort in one study. However, estimates may be unreliable, and sources of data, and methods of analysis (e.g. life tables vs product limit Kaplan-Meier) should be checked [108].

In 1992 McClellan reported an increasing fatality rate with age: 8.6% in patients aged 20 to 45 vs. 17% in those aged 46 to 65, and 24.1% in those aged over 65 years [9; 66].

In the 1991 EDTA Report it was found that after careful analysis, "a relatively constant 16-19 fold increase in mortality exists in renal replacement therapy patients compared with the general population in the UK and Italy" [110].

The WHO HFA Database of cause-specific standardised mortality rates does not contain information on end-stage renal failure as a specific cause of death [2]. Also the use of population mortality rates as indicators of the wider morbidity of renal failure is controversial, particularly because end-stage renal failure is seldom given as cause of death amongst people on renal replacement therapy [9; 107]. Despite these difficulties, in Australia chronic or unspecified renal failure was reported as being the 7th leading cause of death in 2000. Other studies have also

reported kidney disease as an endpoint on death certificates since 2001 [2; 127] and references in Table 2.4.

In a report from Romania in 2003, 1- and 5- year survival rates were surprisingly high at 91% (95% CI 89 to 92%); and 62% (95% CI 59 to 65%). Diabetic nephropathy accounted for 13% compared to 2% in 1997 [122]. Previous European data shows that predictive survival models have a low accuracy, especially for 1-year information [128].

2.8.2 Causes of death for patients with CKD5 on RRT

Although CKD5 is seldom registered as the cause of death, analyses of proportional mortality from the USRDS and EDTA Registries indicate that in 1990 cardio-vascular disease accounted for 36-53% of deaths as primary cause or as a co-morbid condition if the onset of cardio-vascular disease was registered later than the diagnosis of end-stage renal failure. The main causes registered are complications of the disease. These were myocardial ischaemia and/or infarction (more common in transplant patients) followed by cardiac failure and cardiac arrest in HD patients, and then cerebro-vascular and "other cardiac" [110; 118; 124]. Infections account for approximately 12-19% of deaths, primarily for transplant patients also for dialysed (peritoneal) patients [124].

Approximately 25-35% of deaths are accounted for by causes registered as "others". This pattern of causes of death among end-stage renal failure patients has changed recently with a breakdown into: "social deaths" (suicide, withdrawal) accounting for 5-12%, and 10-12% remaining "unknown" causes of deaths. In the Dialysis Outcomes and Practice Patterns Study (DOPPS), depression was independently associated with higher risks of mortality and hospitalisation among HD patients, both in the USA and Europe [114; 115].

Some researchers argue that the registered cause of death following medical certification of cause of death (MCCD) is biased. Deaths from cardio-vascular diseases could be overestimated among end-stage renal failure patients, and deaths from its progression and its consequences could be underestimated [129].

Perneger and others stress the importance of validity, reliability and concordance of information in relation to different sources of data [127, 129, 130, 131, 132]:

> "Selection of a cause of death in end-stage renal disease patients deserves more attention from renal disease nosologists and information managers. Adjustments to the Renal Data system database may include coding of multiple cause-of death data and separate reporting of cause-of death and quality control information. Clarification of ICD-9 coding (note: by 2010 this is ICD-10) for kidney diseases is also warranted. Increased compatibility between the two information systems may greatly increase their usefulness…….[A] plausible explanation is that death certificates and registry reports do not measure the same concept of 'cause of death'. The registry reporting system emphasises possible indicators of quality of care [withdrawal from therapy, vascular access haemorrhage, or hyperkalemia]...which may be poorly reported on standard death certificates. These are mechanisms of death rather than underlying causes." [133]

European Registry data also suggest that total and cardio-vascular mortality is higher in Northern than in Southern Europe, and this was confirmed by an in-depth age-stratified analysis of myocardial ischaemia and infarction as causes of death in the UK and Italy [110].

One other explanation of cardio-vascular factors being often recorded as causes of death in patients undergoing renal replacement therapy could be the most frequently recorded primary diseases leading to end-stage renal failure: hypertension and diabetes mellitus. These conditions can develop cardio-vascular complications independently of the alteration of the renal function, and for this reason the cause of death can be misclassified [97].

Other data show that total and cardio-vascular mortality in patients with end-stage renal failure due to diabetic nephropathy show higher rates than in non-diabetic patients (standardised rates for age, sex, cardio-vascular cause of death). With information being not directly comparable from various sources conclusions are difficult to draw [130, 131].

Currently there is no information on registered causes of mortality for patients with end-stage renal failure in Romania.

2.9 Intermediate (surrogate) outcomes

The large and unstructured literature does not clearly distinguish between different types of complications (nosocomial infections, vascular access complications, etc) developed by patients

with CKD5 under renal replacement therapy (RRT). It often refers only to 'RRT- related complications'. However, any complications developing after treatment started could be:

- an event due to the primary cause which led to end-stage renal failure, and/or
- an event due to some co-morbidity, and/or
- an event due to the renal replacement therapy (RRT).

Literature searches were grouped into infectious and non-infectious complications. Both types can be encountered in HD, CAPD and transplant patients. They can also be explored indirectly through other indirect intermediate outcome measurements such as hospitalisations. However, given the very limited data available from Romania, this part of the critical appraisal of the literature was not pursued in any more depth.

2.10 Quality of life

In the dawn of the renal replacement therapy era both patients and professionals focused on adding years to life. Levy quotes a landmark paper[134]:

> "The absence of behavioral observations in the very early days of dialysis is underscored in the 1964 presidential address of Belding Scribner to the American Society for Artificial Internal Organs: 'Because patients and physicians were allies in a continual fight for survival, there was no time to worry about much else. Patients were basically happy, and the dire predictions of emotional breakdowns and suicide made so easy because of the ever-present arterio-venous shunt usually did not materialize. As long as the struggle for survival was the main issue, emotional problems were suppressed."

However, nearly forty-five years on, quality of life, or health-related quality of life, ultimately counts more for the chronic patient than simple survival. It is a multidimensional construct and it includes life-satisfaction, self-esteem, health and functioning, socio-economic status and social role [135].

Research in this area, in respect of patients on renal replacement therapy, goes back to 1971, when the psychosocial aspects of patients on dialysis and kidney transplantation began to be addressed. However, it took researchers decades to develop and apply a range of reliable and valid quality-of-life indicators. Now a wide range of instruments is available. The most widely used in patients under renal replacement therapy are [136]:

- the SF-36
- the Karnofsky Performance Scale (KPS)
- the Kidney Disease Quality of Life (KDQOL) as a disease specific instrument (KDCS in short); and
- the Spitzer QL-Index.

Other instruments that have been used include the Nottingham Health Profile (NHP) and the Sickness Impact Profile (SIP). Some authors have suggested that for renal patients under renal replacement therapy and associated renal anaemia the NHP provided a "measure of perceived health" and the SIP provided a more "functional measure"[137].

Health-related quality of life specialists and researchers attach different meanings to the term when it comes to its measurement[138]. In particular, health psychologists and some researchers prefer to look at health-related quality of life (HRQoL) with either generic (all aspects of health, all health conditions) or specific tools (e.g. Cognitive Depressive Index- CDI, Kidney Disease Quality of Life -KDQoL). Some prefer to use health profiles (e.g. SIP, NHP, SF-36), some to use more than one instrument [139, 140]. They also use measurements of compliance with treatment. SF-36 has been widely used since 1995. Health economists, on the other hand, use HRQoL measures from the perspective of utility or 'preference' measures, often based on satisfaction with life (e.g. EuroQoL/ EQ-5D) for cost-utility studies.

The SF-36 was once validated in Romania (general population) in the mid 1990s [141] and the questionnaire was used for the first time in haemodialysis patients in 2000 with results published in 2004 [142]. Another study was published in 2008 [143]. The summaries of the physical components score and the mental components score, or PCS and MCS scores, from the single centre study were 42.6 ±18.9 and 46.3± 21.1; the 2008 reported results from a multicentre study (12 RRT centres) showed values of 46.3 ± 19.2 and 55.1 ± 19.3 (cut off points of 43 and 51 were chosen and 64.4±21.1 and 63.8±22.5 were the Romanian general population norms respectively published by Mihaila et al in 2000 [141]; the kidney disease components score or KDCS score showed a value of 68.3 ± 11.3 (with no other reference).

Dutch researchers led by de Wit looked at the value of using both profiles (SF-36 and EuroQoL/ EQ- 5D) and preference-based measures such as the standard gamble (SG) and time trade-off (TTO) in dialysed patients. They concluded that:

> "Health profiles and health preferences represent different aspects of HRQoL. An impaired health status may not be reflected in the preference scores. Coping strategies and other attitudes towards health may affect the preference scores more than they influence health profile outcomes. The added value of health preferences methods in clinical research is limited." [144]

Salek gives a very comprehensive list of over 40 QoL instruments that have been used with peritoneal dialysis patients [145]. However, none of them were specifically developed for this purpose (CAPD).

The tendency recently has been to measure QoL with at least two instruments; one generic and one disease specific, which makes the measurement of quality of life almost an independent area of study. The most commonly used generic instrument with patients on renal replacement therapy is the SF-36. It is easy to apply whether by the patient or an interviewer, easy to compute scores on its 8-item scale, and it allows computation of summary or 'domain' scores, distinguishing for example between mental and physical components, and benchmarking.

Disease specific instruments for end-stage kidney disease have been developed since the 1990s and are still being validated. Hays reported in the mid-1990s from a study which he developed a new renal disease specific instrument: the KDQoL. It uses a 36-item health survey scale (the RAND version), as a generic core combined with 11 kidney disease-targeted grouped scales (KDCS) and when expanded in analyses, reporting on a total of 107 items is possible. In general, the instrument looks promising, but there are possible difficulties with its application and hence a Romanian version was validated very late for this research, in 2007 [146, 147]:

- it is complex, and validation in languages other than English will take a long time;
- its length and variety of items requires a trained team of interviewers with substantial cost implications.

Two disease-specific instruments are the Kidney Disease Questionnaire (KDQ) and the Renal Quality-of-Life Profile (RQLP). At the end of 2008, there was little information on the internal

consistency, reliability and translation of these two instruments. Therefore disease specific measures pose major problems in their application [144].

To summarise, the impact of treatment on quality of life from the literature shows that:

- The health-related quality of life of patients undergoing renal replacement therapy is a very important outcome, responsive to quality of care, and a good deal of effort has been put into developing instruments for measuring it [34; 91; 135; 144];
- For some dimensions of health–related quality of life, transplantation gives similar values to those in the general population [92; 140];
- For most dimensions of quality of life patients on hospital HD or continuous ambulatory peritoneal dialysis score lower than the general population or transplant patients [34; 91; 141].

In the Romanian study from 2008, the physical components score (PCS) and mental components score (MCS) in haemodialysed patients were again lower than in the Romanian population, but compared with two international studies the outcomes appear significantly better [122; 143]. These results seemed inconsistent with survival analyses and results from the single centre study by Covic et al (2004) which had a poorer MCS score than the multicentre result (46.3 vs. 55.1), despite patients being younger (48 years vs. 52 years) [142]. As for the comparison with international values, one explanation could be that Romanian HD patients were overall younger than their Western counterparts.

The study of QoL needs to be further reproduced for establishing a reliable baseline and further with individual patient trend, rather than sub-sampling a cohort of patients [141]. Also, standard deviations were similar in all 3 studies: general population (sample of 1,192, representative 18 years and above), single centre (82 patients, mean age 47.9 ±12.1 years) and multicentre (709 patients, mean age 51.7±12.6 years). The general population sample was randomly selected, only once [141] and the renal patient samples are subsequently self-selected, thus comparison in scores is difficult. This merits further attention when scores are measured and compared [142, 143].

Unfortunately it was not possible to collect primary data on quality of life outcomes for RRT in Romania as part of the current study.

2.11 The burden of chronic kidney disease

2.11.1 Chronic kidney disease (CKD): prevalence

The relative burden of chronic kidney disease is measured as a prevalence rate. In a study based on primary care records in SE England, Stevens et al reported the % prevalence rates for chronic kidney disease stages 3-5 given in Table 2.8. A Romanian study of two regional renal biopsy databases showed results from a 10-year period (1995-2004) on prevalence of biopsies which were analysed at 11/per million population/ year for two Romanian regions (6 million population) and the proportion (%) of CKD was 10%; the MPGN (membrano-proliferative glomerulo-nephritis) as an important CKD precursor showed a substantial decline during the period [148].

Table 2.8: The prevalence of chronic kidney disease stages 3-5 in SE England (Stevens et al 2007 [149] and Australia (Chadban et al 2003)[81]

	Age groups	*18-*	*25-*	*35-*	*45-*	*55-*	*65-*	*75-*	*85+*
England	*Males*	0.01	0.17	0.71	3.08	6.89	17.65	33.16	44.75
	Females	0.18	0.79	2.69	2.79	13.09	27.86	41.68	48.61
Australia	*Males*		0 (0 - 1.0)		1.8 (1.0 - 2.6)		51.8 (47.1 - 56.5)		
	Females		0		3.2 (1.9 - 4.4)		57.2 (51.4 - 63.0)		

2.11.2 CKD3 to 5

Coresh et al [53], in data from the USA NHANES survey 1999-2004, reported a prevalence of stage 3-4 chronic kidney disease of 0.7% for those aged 20-39 and 37.8% for those aged 70+, a marked increase since NHANES 1988-94 (OR 1.47). According to the KDQI definition, the overall prevalence was 13% [38].

In a 2008 press release by the Ministry of Public Health and the National Health Insurance Fund, Romania reported an estimate of CKD of 10% [150]. Specific stages or how this was measured, were not given.

In a study in the south of England Drey et al, defining chronic kidney disease as serum creatinine >150 micro-mol/L for 6 months, found 1,701 cases per million population (pmp) aged < 80 [151]. In Australia Chadban S, et al 2003 reported the figures shown in Table 2.8 [55].

2.11.2.1 CKD5: incidence and prevalence

In the United States the Renal Data System (USRDS) has provided a focus for the collection and analysis of information on the incidence, prevalence, treatment and mortality for end-stage-renal-disease in the USA ever since the mid-1980s [9; 109]. The European Dialysis and Transplant Association - European Renal Association (EDTA-ERA) has had a similar history, except that it was only in late 1995 that the new constitution embraced the epidemiological along with the clinical aspects of end-stage renal failure and its treatment [3]. The ICD-9 panel revisited chronic kidney disease end-stage renal disease and recommended new coding to be introduced from January 2007, but so far no reports have been produced based on the new codes [132].

It is very difficult to capture all incident cases, and the literature usually reports the number of new patients *beginning treatment* for end-stage renal failure during a certain year. However, American and European terminologies differ. In the USA, 'reported incidence' is taken as synonymous with starting on renal replacement therapy, on the basis that all newly diagnosed cases will be offered a treatment immediately they reach stage 5 [9; 125]. In Europe 'acceptance' excludes incident cases who are alive but not on renal replacement therapy, recognising that there may be unmet incident or new need, detected or not. Incidence may be expressed as *crude* rates (new end-stage renal failure patients per million population per year); or as *specific* rates for population subgroups (by age, sex, area of residence, etc., and combinations of these) [9; 53; 78; 110; 125; 152].

Incidence rates can also be based on population screening, or inferred from pre-diabetic conditions such as impaired fasting glucose (IFG) and searches of routinely collected general practitioners' (GP) computer data. Screening should generally increase detection rates [70; 90; 153]. GP and Register data can be used for triangulation. The latter includes specialist diagnosis, including biopsy information in cases when biposy is performed [148].

The number of patients with CKD5 within a given year provides an indicator of 'prevalence' (USA) or 'stock' (Europe) although this may only be the tip of the iceberg of the actual prevalence (see Section 8.1). Conventionally, and in line with the definition in section 1.2, stage 5 includes only patients who have completed at least 90 days on treatment, either in a dialysis programme or with a functioning kidney transplant [107]. In recent years eGFR measurements at GP level led to high CKD prevalence estimates in the general population in the UK and fears of an increase in needs for treatment [154]. However, other researchers followed-up over 3,000 individuals with

sustained reduced eGFR and discovered that the epidemiology of CKD 3b-5 is complex and that, individual risk (incidence of a defined stage), then relative risk and absolute risk are important measures when assessing the epidemiology of the condition over a period of follow-up [155]. They identified in the followed-up cohort of more than 3,000 patients with CKD3 and above, that: 5% required and initiated RRT during the 6 years of follow-up, 59% died without initiating treatment and that 36% did not require RRT at the end of the 6 years and remained under observation. This merits further attention when considering the age and case-mix at initiation of treatment.

The definition in section 2.3 consists of: at least one co-morbidity, such as: anaemia, gastro-intestinal disorder, neurological disorder, cardio-vascular disorder or raised blood pressure (≥ 140/90 mm Hg). In Romania, unless the end-stage renal failure patient was known to the renal specialist prior to entry on renal replacement therapy, discriminating between a primary renal disease, hypertension and/or diabetes mellitus as a precursor when the patient presents with end-stage renal failure remains a problem and this makes the condition's staging difficult even though most patients would have reached stage 5 at this point and would also have at least one co-morbidity [9; 11].

In this study the terms incidence and prevalence will be used to cover the spectrum of chronic kidney disease (CKD), and acceptance and stock for CKD5 on renal replacement therapy (RRT)[1]. Table 2.9 sets out the main epidemiological indicators. CKD covers stages 1 to 5 and CKD5 is the stage when renal replacement therapy is required.

[1] Since stock ≈ acceptance *survival, changes in case-mix, technology or capacity in a treatment facility can affect stock in two ways: an increasing acceptance rate on RRT (with expansion of facilities and/or their capacities); or an increase in survival of those treated.

Table 2.9: *Epidemiological indicators of CKD and CKD5 on RRT*

Indicator	*Formula*
CKD Incidence (risk, cumulative incidence, any stage)	New patients with CKD/ Population at mid-year * 10^6 for a given year
CKD5 Acceptance (rate, newly on RRT)	New patients with CKD5 on RRT/ Population at mid-year * 10^6 for a given year
CKD Prevalence (rate)	New and old patients with CKD at 31 December/ Population at mid-year * 10^6 for a given year
CKD5 stock (rate, all on RRT)	New and old patients with CKD5 on RRT at 31 December/ Population at mid-year * 10^6 for a given year

Table 2.10 presents results from some population-based epidemiological studies, first reported 25 years ago by Challah and Wing, mainly involving comprehensive, primary care data on chronic renal insufficiency (CKD) and end-stage renal disease (CKD5) [90], and some more recent surveys [77; 156, 157]. This table summarises studies which have been considered at the conceptualisation of the research as the approach in designs underlie a public health approach to renal disease.

Table 2.10: Epidemiological studies of the incidence and prevalence of ESRD

Ref	*Country*	*Setting & Methods*	*CKD Incidence (pmp)*	*CKD Prevalence (pmp)*
90	United Kingdom 1971	400 beds hospital (urea>71 mg%)	39 (<60y & appropriate for dialysis	
	Northern Ireland 1972	GP questionnaire (urea>100 mg%)		424 CRF/3y & 222 CKD5/3y
	Scotland 1972	GP questionnaire (urea>100 mg%) and death certificates	52 (<65y & appropriate for RRT)	
	S-E Scotland 1973	GP questionnaire (urea>100 mg%)		190
	England 1975	Pathology register (urea >100 mg%)	45 (<65y & appropriate for RRT)	
	England (Devon and Blackburn) 1990	Pathology register (serum creatinine >500 µmol/l) over 2 years	148 117 (>70 years) 58 (20-49 years)… 588 (> 80 years) 78 initiated on RRT	
156	France (INSERM study) 1992	Various sources: -mortality statistics -sickness fund -PMSI -EDTA	75	409 (1982 206)
157	Ile-de-France (1998 data)	Special form (all patients entering RRT including Failed transplants)	100 - 14 (< 18 years) - 55 (18-39 years) - 100 (40-59 years) - 190 (60-74 years) - 259 (≥75 years) 108 including failed Tx	417 to 433 (3.8% increase over one year)

Table 2.10 shows how old the community based studies of the incidence and prevalence of chronic renal insufficiency are, with most of them from the 1970s. Stages 3-5 of chronic renal insufficiency are difficult to measure, and such studies are difficult and expensive, making the real burden of renal *disease*, with renal insufficiency in all stages 1-5 (i.e. not just those on renal replacement therapy or stage 5) very difficult to determine. Also these studies give a wide range of values that are difficult to compare, with differing age-groups and typically without a common or standardised methodology. One study has followed up patients with CKD 3b-5 for 6 years and although it looked prospectively at assessing the CKD staging through eGFR, only about 40% of patients were alive at the end of follow-up, thus making it even more difficult in assessing lifetime indicators [118; 155].

A paper on the progression of chronic renal failure by Yu, 2003 describes in detail an updated review of known, but multiple, factors which contribute to the evolution of chronic renal failure showing that many complex associations between exposure factors remain to be explored [158].

In 2006, the Incident ESRD Study Group published one paper in an attempt to provide better estimates of the incidence of ESRD, by capturing all new cases in countries where access to treatment to publicly funded renal replacement therapy was restricted only by medical contradictions and not by socio-economic or geographic circumstances. The recording of incident cases was believed to be complete for persons normally resident in the country or region [152]. A summary of results is shown in Table 2.11.

Most recently, CKD and its stages are measured with eGFR, thus defining the prevalence in various populations. The latest formulae are those developed by the MDRD Study and the CKD-EPI Collaboration. These were briefly described in the clinical definition of CKD, in Section 2.3.1.

Table 2.11: Incidence of CKD5 in European population [152]

	All diabetic CKD5				*All non-diabetic CKD5*			
	30-44 years		*45- 64 years*		*30-44 years*		*45- 64 years*	
	ASR	*99% CI*	*ASR*	*99% CI*	*ASR*	*99% CI*	*ASR*	*99% CI*
Lowest value	7	5 to 9 (Netherlands) 2-13 (Spain, Basque Reg)	20	15 to 27 (Norway)	26	20 to 33 (Finland)	95	83 to 106 (Finland)
Highest value	36	29 to 45 (Finland)	70	62 to 79 (Austria)	50 53	44 to 57 (Greece) 43 to 64 (Spain, Valencia)	132 182	119 to 146 (Belgium, Flanders) 163 to 202 (Spain, Valencia)

ASR = age and sex standardised [incidence] rate (pmp)

Furthermore, established databases in Europe (ERA-EDTA), USA (USRDS), Australia and New Zealand (ANZDATA) have also published estimates of acceptance and stock. These are summarised in Table 2.12 [9; 11; 117]. Since the 1990s the primary research effort has been directed towards better information on the leading causes: primary renal disease, hypertension, and diabetes mellitus and to allow for benchmarking, which may only have been successful from as recently as 2007.

Table 2.12: Measures of acceptance and stock for end-stage renal failure under renal replacement therapy world-wide

Ref.	*Area*	*Year*	*Acceptance (Rate pmp)*	*Stock (Rate pmp)*
EDTA-ERA [152]	Europe	1992	79.1 median (9.4-118.2)*	437 median (28-579)*
ANZDATA [37]	Australia	1992	79	482
	New Zealand	1992	105	450
USRDS [35]	USA	1993	214**	824***
Lok CE [82]	Canada	2001	1,300 diabetic ESRD 110 non-diabetic ESRD	n/a
DH [40]	UK	1998	96 (76 to 128)˜	529 (439 to 693)^
Romanian Register [27]	Romania	1996	20	57

*Ranges of acceptance and stock within the EDTA Registry; ˜Anglia Oxford Region and Wales;^ Northern Ireland and North Thames.

** Reported incidence; not called acceptance;

***Stock is prevalence in the USA renal replacement therapy

In Table 2.12 the Canadian acceptance rate (incidence) for diabetic CKD5 was the highest found in the literature and measured by a prospective observational study [56]. However, this is also an estimate assessed after 2000, whereas most other studies assessed theirs in the early 1990s.

There are similar increases in overall incidence or acceptance of end-stage renal diseases in various European populations, For acceptance standardised rates (ASRs) in diabetic CKD5 in the 30 to 44 year olds, the Netherlands has the lowest value (7 pmp) and Finland the highest (36 pmp). Finland has a high prevalence of diabetes in the general population (3.3%) and close to that of 4% in Romania. For non-diabetic end-stage renal disease, Finland has the lowest values of ASRs in both reported age groups: 26 pmp in 30 to 44 year olds and 95 pmp in 45 to 64 year olds. The highest values were reported from 2 Mediterranean countries as 50 pmp and 182 pmp respectively, in same age groups [78; 149].

Incidence and prevalence as well as acceptance and stock are technical indicators and reflect exclusion or inclusion on RRT. These become comparable when measured in various populations only when numerators and denominators are clearly defined. This is for example reflected in the

variation of CKD from 4 to 11% from a 2010 review [159] and the variation noted in acceptance and stock in various countries (Table 2.11).

Acceptance and stock (CKD5 on RRT) were low in Romania in 1996: 20 pmp and 57 pmp when the European median values were 79 pmp and 437 pmp in 1992; the UK figures were 96 pmp and 529 pmp in 1998 (i.e. an acceptance four times higher and a stock ten times higher than in Romania) [122; 160].

2.12 Prevalence of precursors

2.12.1 Diabetes

Data on regional variations and trends in the precursors of kidney disease can be useful for estimating the current and future prevalence in Romania [70; 78].

In the USA the prevalence of diabetes in the general population rose from 4.9% in 1990 to 6.5% in 1998 [81, 82]. In another study in the USA from 2002, the disease prevalence was 6.3% in the general population, with <5% in the 20-39 years age group, 7-18% in the 40-59 years age group, and 13-30% in the ≥ 60 year olds. The figures were higher in black, Hispanic, and American Indian groups than in the white population [35; 58]. The American trends, by major age groups, are shown in Table 2.13.

Table 2.13: USA trends in the prevalence of diabetes mellitus

	Year	*25-44*	*45-64*	*65-74*	*75+*
White men	*1984*	0.6	4.6	8.5	9.3
	1994	0.7	5.7	10.7	10.7
	2004	1.2	9.8	20.2	16.4
White women	*1984*	0.7	5	9.2	8.3
	1994	0.8	5.3	10.2	9.9
	2004	1.4	8.3	14.6	13.5

Data from England and Wales are summarised in Table 2.14 [46]. The overall figures for the Health Survey of England (HSE) in 2003 were 4.3% for men and 3.4% for women. (Furthermore 3% of men and 0.7% of women above the age of 35 years were found to have impaired fasting glucose (IFG)). In 1999 the UK Joint Health Survey Unit reported prevalence rates for England and Wales of <0.5% for type 1 diabetes and 3% for type 2 diabetes, so that type 2 represented 90% of all

diabetes cases [46,47,48]. Results from the two 2003 UK studies appear consistent. However the 2003 results show a nearly 3-fold increase in 35-44 year old men for 2003 compared with 1994, and a 30% increase in men aged 55+ years; for women, the overall estimate nearly doubled from 1.9% to 3.4%.

Comparing the UK and USA data for those aged 45- 64, the white male American population in 1984 had a rate (4.6%) which was twice as high as the UK male rate in 2001 (2.2%); and results for women showed a three-fold difference (5% compared with 1.5%). Comparing the USA in 2003 with the UK in 2003, rates in the 65-74 year olds were still higher in the USA: 20.2% and 14.6% compared with 11.9% and 8.4% in the UK.

Table 2.14: Summary of UK prevalence studies for diabetes mellitus

Prevalence %	*Source*	*16-24*	*25-34*	*35-44*	*45-54*	*55-64*	*65-74*	*75+*	*Overall*
Men	*HSE 1994*	0.8	0.8	1	2.5	6.4	5.8	*7.5*	*2.9*
	HSE 1998	0.1	0.7	1.6	2.9	5.8	7.0	*8.7*	*3.3*
	GPMS 2001	0.24	0.49		2.17		4.28	*4.75**	
	UKPDS 2003	<1	<1	2	3	6	7	*9*	
	*HSE 2003***	0.4	0.3	2.8	3.6	8.1	11.9	*10.0*	*4.3*
	*HSE 2006***	0.8	1.2	2.4	6.0	8.5	15.7	*13.5*	*5.6*
Women	*HSE 1994*	0.6	0.3	0.9	1.5	2.5	4.8	*5.2*	*1.9*
	HSE 1998	0.8	0.7	0.9	1.6	3.1	6.6	*6.6*	*2.5*
	GPMS 2001	0.15	0.34		1.54		3.37	*3.74**	
	UKPDS 2003	<1	<1	1	2	3	11.9	*10*	
	*HSE 2003***	*0.9*	*0.9*	*1.5*	*2.6*	*4.7*	*8.4*	*8.9*	*3.4*
	*HSE 2006***	*0.9*	*1.2*	*1.2*	*3.6*	*6.0*	*10.4*	*10.6*	*4.2*

* 75-84 years ** weighted

Figures published recently by the European Commission show the population prevalence of diabetes mellitus in different countries ranging from 3.3% in Finland to 7.3% in Cyprus [48].

In 2008 an estimate for the Romanian population was published and reported in the media by the Romanian Ministry of Public Health for the year of 2007. The numbers of cases in the general

population were given as up to 570,000, of whom 2,500 were under 15 years old. This implied disease rates of 3.4% in the general population and up to 5.5 per 100,000 in the 0 to 15-year-olds. These figures were confirmed by a paper reported from the EuroDiab survey [161]. The prevalence of diabetes mellitus in Romania (2008) is thus estimated to be around 4% [162]. The Romanian rates in the younger population ranged from 1.43/100,000 in 0-4 years to 4.37/100,000 in those aged 10-14 years. Geographically, the north-west of the country has seen an increase between 1988 and 1997 [162].

To summarise: estimates of the current prevalence of diabetes mellitus rank Romania lower than the USA, but similar to other Western European countries. Impaired fasting glucose (IFG) data and proportion by type of DM were not available from Romania for the adult population of over 15 years. Romania consists mainly of white individuals and no data were available for ethnic minorities.

With regard to trends in diabetes, there are limited data for Romania; point prevalence rates have been measured in national health surveys and increased from 2.7% in 1989 to 4% in 2007. The estimates from the Health Insurance Fund for 2003, 2004 and 2005 were 1.98%, 2.12% and 2.23% respectively. Part of this increasing trend may be explained changes in the structure of the population [122; 147; 161, 162; 163]. The percentage of patients on renal replacement therapy with diabetic nephropathy rose sharply from 1% in 1997 and to 13% in 2003, but this is still is lower than the 19% recorded in the UK in 1998 [60] and can be expected to increase further. More details are given in Chapter 3.

2.12. 2 Hypertension

The prevalence of hypertension varies widely geographically and increases with age [164, 165, 166, 167]. Table 2.15 from the US NHANES survey, Table 2.16 from the Health Survey for England and Table 2.17 from two studies in Spain all show this age-related increase, starting younger for men than women but converging by the age of around 65.

Table 2.15: Hypertension: on treatment or > 140/90 mm Hg in the USA (NHANES) [168]

	Period	*20–34.*	*35–44*	*45–54*	*55–64*	*65–74*	*75+*
Male	*1988–1994*	7.1	17.1	29.2	40.6	54.4	60.4
	2001–2004	7.0	19.2	35.9	47.5	61.7	67.1
Female	*1988–1994*	2.9	11.2	23.9	42.6	56.2	73.6
	2001–2004	*2.7	14.0	35.2	54.4	72.9	82.0

Table 2.16: *Hypertension: controlled or uncontrolled*[2] *in England (HSE)* [167]

			16-24	*25-34*	*35-44*	*45-54*	*55-64*	*65-74*	*75+*
All with high blood pressure	*Men*	*1998*	16.0	20.5	26.1	42.3	59.8	69.9	72.8
		2003[e]	10.5	13.3	21.2	37.1	53.0	65.3	67.2
		2003[f]	6.4	11	19.5	34.7	50.6	64.1	64.4
		2008	7.5	12.5	17.9	32.9	52.1	61.6	68.4
	Women	*1998*	4.2	6.9	13.2	30.8	51.6	72.8	77.6
		2003[e]	1.9	4.9	10.2	24.5	47.1	68.1	77.2
		2003[f]	1.9	5.2	11.3	23.4	46.5	64.3	74.9
		2008	1.9	5.3	13.4	24.6	41.5	61.6	73.0

Table 2.17: Hypertension in Spain (Banegas 1998[169]*, Ramos 2004* [166]*)*

HT (%)	*All*	*Men*		*Women*	
Age group	35-64	25-54	55-74	25-54	*55-74*
Hypertension	47	19	53	12	*60*
Treated hypertension	n/a	3	22	6	*27*

[2] The top part of the table includes those with a history of hypertension but whose blood pressure is being controlled by treatment; the bottom part is those whose blood pressure is high, including some who are on treatment for it.

The US rates in the period 1988 to1994 appear to be much lower than those for England in 1998, except in the 75+ age group. However by 2003 the English rates had dropped and the American rates had increased to slightly above the English rates. It is possible that some of these changes may be due to blood pressure measurement bias, but some may be attributable to other factors, such diet and smoking and exercise.

The Spanish studies report much lower values than either England or the US. Precise comparison is impossible because the classification of age groups is different. Also some of the differences in reported prevalence may be attributable to different methods of measuring blood pressure.

The European Commission's 2007 report on major and chronic diseases gives data on the prevalence of hypertension in European countries, summarising studies from 1994 to 2003 [62]. Different studies used different definitions of hypertension as well as different methods of data collection such as questionnaire administration or physical measurement. However these studies and a WHO database suggest that the prevalence of hypertension doubles after the age of 50 years in line and that 50% of the population will be hypertensive after age of 55 years [54; 65; 162; 165,166].

For Romania the source of the prevalence data in the European Commission report was the WHO MONICA study for 1997 [2; 62]. The prevalence of hypertension for the population aged 15 to 64 years was reported as 4.9% in men and 4.5% in women. In 2008 the Romanian Ministry of Public Health also reported levels of around 6.5% in the general population for 2006 [162].

Rates of hypertension by JNCI-VII stage were not available from any of the Romanian sources, although recording of general information on hypertension was started in 2003 by the Ministry of Public Health after a gap since the latest MONICA WHO study which recorded Romanian data for 1997 [163]. The MoH data reported overall prevalence rates in the general population of 6.6% for 2004 and 7.1% for 2005. There is no reported breakdown by age and sex, but there has clearly been an increase since 1997. In broad terms these are similar to the UK rates.

2.12.3 Obesity

The link between obesity, diabetes and chronic renal failure were shown in Table 2.4. Data on this are limited for Romania [170] as 7.6% for men and 9% for women (BMI>30, all ages). It is assumed that similar risks would apply across the Romanian population.

The US 1999-2002 National Health and Nutrition Examination Survey (NHANES) indicated that 10% of 2-5 year olds and 16% of 6-19 year olds were overweight [69], and that 18% of the 12-19 year olds had Impaired Fasting Glucose (IFG) test results signalling pre-diabetes (insulin resistance) status [171, 172].

Table 2.19 gives data on obesity in the USA, England and Romania from national health interview surveys. A BMI greater than 25 is generally considered overweight, and greater than 30 obese (see Section 2.4.2 on Diabetes and 2.4.4 on Obesity).

To summarise:

- levels of overweight and obesity in the USA have increased markedly since the 1970s, and continued to increase until around 2000. Obesity in women has changed relatively little since then; obesity in men seems to have levelled off if around 2005-6 [63; 167,168;
- this has also happened in England. Current levels of obesity in men are very similar to those in the USA, but for women American levels are higher in all age groups except those aged 75+;
- although England has much higher levels of actual obesity (BMI > 30) than Romania, the levels of overweight (BMI > 25) are of similar orders of magnitude;
- levels of obesity in England have increased markedly between 1994 an 2003 in all groups except older women.
- Romania is benefiting from a cohort of people aged 75 or more that are less likely to be overweight than any other group aged 35 or more. Later cohorts are more likely to be obese.

A summary of this information is shown in the table below (Table 2.18), with more detailed information in Tables 2.19 and 2.20:

Table 2.18: Summary of condition precursor prevalence rates in 3 populations:

	DM	*HT**	*Obesity*	*Smoking*
USA	*7*	*30*	*30*	*25*
UK	*3*	*25*	*23*	*23*
Romania	*3*	*16*	*10*	*33*

**Note: most unreliable parameter*

Table 2.19: Body Mass Index for the USA, England and Romania

				15-24	*25-34**	*35-44*	*45-54*	*55-64*	*65-74*	*75-84*
BMI >25	*Men*	*USA*	*1976–80*		41.2	57.2	60.2	60.2	54.2	---
			1988–94		47.5	65.5	66.1	70.5	68.5	56.5
			2001–04		59.0	72.9	78.5	77.3	76.1	66.8
		England	*1994*	30.4	49.6	61.7	67.9	69.2	71.0	62.9
			2003	31.8	59.5	71.9	75.8	77.1	77.5	70.7
		Romania	*2000*	17.2	39.6	52.9	61.0	57.3	53.2	40.0
	Women	*USA*	*1976–80*		27.9	40.7	48.7	53.7	59.5	---
			1988–94		37.0	49.6	60.3	66.3	60.3	52.3
			2001–04		51.6	60.1	67.4	69.9	71.5	63.7
		England	*1994*	28.2	37.6	44.8	54.1	64.2	66.0	52.4
			2003	32.1	47.1	55.2	59.1	66.8	71.4	66.5
		Romania	*2000*	8.0	26.0	43.0	54.8	54.9	48.7	34.9
BMI >30	*Men*		*1976–80*		8.9	13.5	16.7	14.1	13.2	---
			1988–94		14.1	21.5	23.2	27.2	24.1	13.2
			2001–04		23.2	33.8	31.8	36.0	32.1	19.9
		England	*1994*	5.7	9.8	15.5	17.2	17.8	17.9	14.7
			2003	8.6	17.8	25.0	28.1	26.8	28.7	20.9
		Romania	*2000*	0.6	5.7	9.8	11.7	10.5	9.7	5.2
	Women	*USA*	*1976–80*		11.0	17.8	19.6	22.9	21.5	---
			1988–94		18.5	25.5	32.4	33.7	26.9	19.2
			2001–04		28.6	33.3	38.0	39.0	37.9	23.2
		England	*1994*	7.9	12.9	16.9	17.8	25.5	25.3	16.3
			2003	13.3	18.7	21.7	26.5	27.8	29.9	26.1
		Romania	*2000*	1.2	5.3	10.6	15.5	14.9	11.2	8.7

* 20–34 for the USA data.

If subsequent generations of older Romanians follow England and most other European countries in their patterns of obesity, it seems likely that the pressure on services for CKD5 in younger age groups will increase markedly as a result [173, 174].

2.12.4 Smoking

Data from interview surveys on current smoking (occasional as well as daily) are given in Table 2.20 [169].

Table 2.20: *Prevalence (%) of smokers: trends in the USA and England*

	Country	year	18–24*	25–34	35–44	45–54	55–64	65-74	75+	Overall ***
Men		1974	40.8	49.5	50.1	41.2		24.3		
	USA**	1985	28.4	37.3	36.6	32.1		18.9		
		1995	28.4	29.9	31.2	26.3		14.1		
		2005	29.7	27.7	26.3	24.5		7.9		26
	England	1984								35
		1994	42	36	31	30	22	21	12	28
		2004	37	37	26	25	19	10	7	24
	Romania	2003	36	52.8				22	9	41
Women		1974	34.0	38.6	39.3	33.0		12.3		
	USA	1985	31.8	32.0	31.0	29.7		13.3		
		1995	24.9	27.3	27.0	24.3		11.7		
		2005	22.6	23.1	22.2	18.9		8.4		23
	England	1984								32
		1994	34	33	28	29	24	19	11	27
		2004	30	29	27	25	20	14	4	23
	Romania	2003	19	21.2				3	4	25

*15-24 for Romania, 20-24 for England ** white men and women for the USA *** for adults

The prevalence of smoking has gone down in young men in England whilst it has remained almost unchanged in the USA. Data from the WHO in 15 year olds and older show the prevalence of smoking is higher in Romania (41%) than the USA (26%), New Zealand (30%) or England (37%). Romania's data show that smoking continues in men aged 25+ with a rate almost double that of the USA or UK figures in the 25-64 years and that is despite a lower uptake of smoking at the age of 15 [175]. For the population of 15 years and older, the World Health Organisation data, show that smoking prevalence for Poland is 44% and Hungary has a 46% rate; these are higher than Romania's [173]. However women, and particularly young ones, smoke less in Romania than American or English counterparts. Thus smoking remains an important risk factor for chronic kidney disease and end-stage renal failure in Romanian men.

2.12.5 Prevalence of risk factors: relative risks and attributable risks

Table 2.18 summarises individual prevalence rates in 3 populations for the 4 main condition precursors. While needs assessment (expressed need and comparative need) refers to possibilities of providing RRT to the Romanian population, epidemiology also goes on measuring not only the prevalence of precursor conditions, but also assess their risk (hazard x exposure) in a given population. This has proven particularly difficult to measure in the case of CKD due to the complexity around precursor conditions: 1. they can act as single hazards; and 2. or as multiple hazards. In either situation the duration of exposure can vary. Epidemiology goes on to assist in this case with indicators such as: relative risk and odds ratio (RR and OR), already covered in the Section of CKD and association with the four condition precursors. Other indicators are PAR% (population attributable risk percent) and the Impact Fraction. These have been used in Chapter 3 to assist with the epidemiological assessments of CKD 5 in Romania and are further discussed in Chapter 9 [174].

2.13 Cost of illness and economic evaluation of treatment for CKD5

2.13.1 Costing frameworks

Romanian data are limited in this area. One paper with mid 1990s data did not report empirical cost measurements, but gave an overall budget estimate for 1993 quoted from a secondary source [176], [177].

Approaches to costing end-stage renal failure in the literature are complex and very varied, and the results probably less generalisable to Romania than some epidemiological parameters [25; 90; 95, 102;159; 178, 179, 180]. However decisions on investment of scarce capital and labour are required, and these require data on costs.

There is no single costing framework recommended by health economists. However, some rules have been universally agreed, e.g.:

- distinguish between direct and indirect costs, and between fixed and variable costs [1].
- include as many types of cost as possible and acknowledge those that are left out;
- consider opportunity costs where available;
- state what the components of each type of cost are; and
- think in terms of the marginal costs of producing more or less of an output.

Economic theory provides a basis for constructing cost functions for any quantity of products or services for which a price is given. From these we can derive marginal economic costs [1].

2.13.2 Economic measurements of benefits

If costs are seen as 'investments' (which could otherwise earn interest, or be spent on housing, education, etc.) then, what is expected in return? What types of benefits are there, and what units are they measured in?

The units of benefit used are:

- natural units (e.g. life years gained) which measure the (opportunity) costs of buying a unit of *effect* (e.g. one year of life gained); or the extra cost of an extra unit of effect;
- utilities (e.g. QALY's - years of life gained weighted for their quality or quality adjusted life years); and
- monetary units (assuming that one life year saved is worth e.g. $3,500). Many different types of benefit (e.g. avoided use of hospital services) can be added together or compared. This type of cost analysis is normally applied at national level (e.g. when choosing between defence vs. education vs. housing, etc).

The type of units chosen defines the approach to economic analysis: natural units for cost-effectiveness (CEA), utilities for cost-utility analysis (CUA), and monetary values for cost-benefit analysis (CBA) [1].

2.13.3 Economic evaluation of renal replacement therapy and related disease management

There have been a number of economic evaluations of renal replacement therapy, some going back to the late 1960s. For the purposes of this study they have been evaluated using 'guidelines for authors and peer reviewers of economic submissions to the BMJ'[181]. Each relevant study should be scored under each of the evaluation criteria[182, 183]. On this basis only one study was been identified as a marginal cost-effectiveness analysis[184]. There are few cost-utility studies; and they have been concerned with secondary prevention of CKD, e.g. due to diabetes mellitus [185]. In theory, economic evaluations should consider opportunity costs but there is only one study which achieved this [186].

Fig. 2.2 presents a general framework of costs adapted from Ehreth [187].

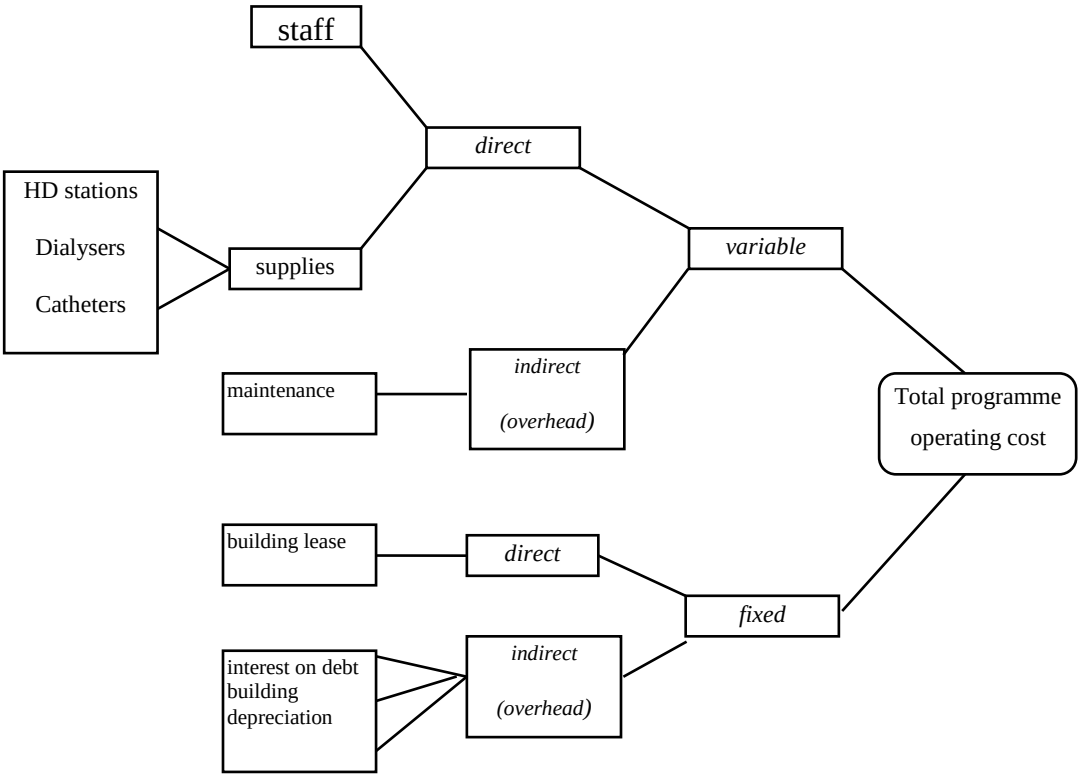
The major weakness which most of these studies suffer from is the lack of good evidence on the relative effectiveness of the different modalities. Also cost estimates change on a continuous basis and vary among countries, depending also on what is measured. However, the literature suggests consistently that the most cost-effective therapy is transplantation (living related followed by cadaver), followed by CAPD, and then hospital haemodialysis [130]. Transplantation provides not only 'best value for money', but also best quality of life for the renal replacement therapy patient. Also, renal anaemia becomes significantly less of an issue under transplantation because the transplanted kidney secretes erythropoietin.

Other forms of therapy, such as the newly introduced continuous-cyclic peritoneal dialysis (CCPD) and automated peritoneal dialysis (APD), or the combination of High Flux- and haemodialysis (HFHD), or haemodiafiltration and classical haemodialysis (HDF vs. HD) although appear effective treatment modality have yet to prove their cost-effectiveness. As with any "new" technology, there is not enough evidence and this will only become available once these therapies have been more widely established.

Cameron refers to estimates of cost/QALY, but these appear to be based on costs from some studies and utilities from others. The UK values for cost/ QALY in the 1980s were: £4,710 for kidney transplant, £19,870 for CAPD and £21,970 for hospital HD [6]. These values would be undoubtedly higher by 2010: a Greek study estimated values of: €60,353, €54,504 and €45,523 per QALY for haemodialysis, peritoneal dialysis and 1st year transplant [188]. A more recent, 2010, Canadian cost-utility analysis showed that the introduction of erythropoiesis-stimulating agents (ESA) or hu-Recombinant erythropoietin or genetically recombined erythropoietin (hu-EPO) for the treatment of targeted renal anaemia levels has costs to the level of (Canadian) $ 96,270 per QALY for low target haemoglobin in CKD patients with or without dialysis. If they were not treated with ESA such costs escalate to $147,980 per QALY [189]. The literature has not updated this indicator, RRT cost/QALY by modality for some time.

When referring to the types of costs measured, the averted cost was mentioned only in those studies of secondary prevention of end-stage renal failure. Studies on tertiary care (i.e. HD, CAPD, etc) do not include such [averted] costs.

Figure 2.2 A programme cost input



A more recent review by Ray surveyed the costs of major complications of diabetes (including end-stage renal disease) in 6 countries. Compared with the costs of treating other complications, end-stage renal disease was most expensive, but varied between the six countries according to mode of renal replacement therapy and year of treatment (year 1 and year 2) as shown in Table 2.21. These are not adjusted for quality of life [190]:

Table 2.21: Costs of renal replacement therapy treatment in Europe (Italy and Spain), Canada and Australia (in €, inflated to 2003 – data on costs from 1998 to 2002)

	Australia	*Canada*	*France*	*Germany*	*Italy*	*Spain*
HD year 1	17,188	58,159	56,487	58,116	43,075	31,233
HD year 2	n/a	93,840	n/a	n/a	n/a	n/a
PD year 1	27,552	33,811	n/a	46,296	n/a	32,706
PD year 2	n/a	47,447	n/a	n/a	n/a	n/a
Tx year 1*	16,246	60,903	24,608	68,175	56,717	28,370
Tx year 2	791	19,986	6,866	10,904	11,582	8,336

* does not specify type of transplant (living donor or cadaveric kidney); n/a= not available

Table 2.21 suggests that:

1) the methodology applied must have differed between countries (Australia has by far the lowest costs); and that

2) both dialysis modalities are difficult to cost during the second year of treatment and beyond; these costs were not available in 5 of the 6 countries. This may reflect the need to target methods of measuring such costs if they are to inform decision makers for policy purposes. From the Canadian figures, the costs of the second year of treatment are very different from the first, HD with a 61% increase, PD with a 40% increase and transplantation with more than a 300% decrease [187;190].

Increasingly, measuring costs of CKD5 and complications is becoming difficult because of the complexity of both leading conditions and the care provided. Conditions leading to end-stage renal failure, such as diabetes mellitus and hypertension, incur costs from the moment of initial diagnosis. Costing a pre-end-stage renal failure stage is very difficult.

Given the heterogeneity in approaches for cost estimation, the question asked was not whether costs were important for this study, but if they were, could they be reasonably measured in order to link this aspect to the treatment model? That is, after having established that, like other parameters for the epidemiological model, costs were also difficult to measure for this model, but worth attempting for the treatment model.

This research has considered accounting costs rather than opportunity costs. However, the dual elements of costing (data from sampled centres) and funding (national programme; reported average costs) were considered separately. There was some limited benchmarking in relation to average costs (reported and estimated by this research).

2.14 Decision support: modelling for health planning and policy in renal replacement therapy

Decision making in the area of renal replacement therapy for CKD5 involves a number of different 'stakeholders'. The main ones are the providers (mainly nephrologists in tertiary care), third party payers (government and other agencies) and increasingly the end-user of the treatment, patients. Nutritionists, psychologists, physiotherapists and other specialised nurses may be involved as well.

Decisions are largely based on clinical grounds, despite the gaps in the evidence base. Since 2005, multi-disciplinary clinics (MDC-care) have had a place in the care of the end-stage renal failure patient, before they enter renal replacement therapy [185]. The value of early referral from general practitioners or family doctors (GPs) to specialists has also been explored in the UK through the new General Medical Service (GMS) contract, but this has raised further questions about the primary, secondary and tertiary interfaces [24;154; 191, 192].

Decision analysis is a widely used technique for informing comparison of strategic options. It is also a useful tool in cost analysis [193, 194].

Decision trees involve mapping out all the possible sequences of events that could occur after each decision 'node'. Given the probabilities of each kind of event and the utilities associated with each end point, expected utilities can then be calculated for each decision option. Similar tree models can be used to estimate the flows down each branch [195].

Examples are:

- a seven-state mathematical model, based on a 26-state Markov chain, of an integrated haemodialysis and transplantation programme[196, 197];
- a model for predicting the future stock of patients on renal replacement therapy due to chronic renal failure in Denmark [198]; etc.

These models have taken acceptance for renal replacement therapy as their starting point.

The literature also describes other types of models, mostly used by management decision makers and third party payers. In the renal field examples, using both acceptance and stock, are:

- static flow models (using stocks and flows) for predicting needs for treatment [3, 4];
- a discrete-time, auto-incremented non-stationary Markov model [199]
- discrete-event simulations of renal replacement therapy [60, 200, 201, 202;
- a system dynamics model used to predict the end-stage renal disease patient population in Japan [203];
- a geographical information system mapping out renal replacement therapy need and provision [204].

Most of these models use advanced programming [60; 198, 199; 201;203; 205], but some, such as those published on behalf of EDTA and most of those for renal disease service planning are based on spreadsheets [3, 4].

All the models are, however, based on defined sets of states and transitions. The main states that are described are: the starting state - acceptance onto treatment; the starting dialysis state, e.g. haemodialysis and related, peritoneal dialysis and related, or a combination; and irreversible or 'absorbing' states: transplantation and death. Transitions (transfer from one state to another) have probabilities (risks) attached to them. These transition probabilities may depend on patients' risk factors (e.g. age, diabetes, etc).

Based on states and transitions, simulations (e.g. Monte Carlo with a 10^n size virtual cohort) are run. Sensitivity analyses indicate the robustness of the model and help interpretation of the results.

Validation of these models is an important issue, often involving comparing model results with historical pattern of change [206].

Such models are vulnerable to errors in both logic and structure, or even:

> "...invalid syntax…the model conditions action on an unobservable disease state and fails to link variables; there is noted failure to apply constant biases, incorrect modelling of the results of a diagnostic test and incorrect modelling of a treatment..." [207].

That is why calibration of the model in the first instance is important; followed by validation.

Nevertheless, using modelling in the area of health services research and resource allocation has advantages. They:

> "...condense reality, as they are trying to understand a complex reality...all analyses, including economic evaluation[s], involve simplification in order to infer something about the real world. The art of model building is to know where and when to simplify"[194].

Data from the literature show that with both discrete simulations and spreadsheet models, estimates of patients in stock can be made; for example in England, both models have been used since the mid 1980s and the latest model for chronic renal insufficiency stages 3-5 was used to predict the number of patients for England, given current stock and acceptance on treatment [86; 196, 197; 208].

In 1996 Berthoux used a spreadsheet model in a French centre; with the input parameters of acceptance and stock of 89 pmp and 453 pmp, the annual dialysis pool expansion rate was estimated at 5.3%, with dialysis patients reaching 55% of the end-stage renal failure pool whilst the remaining 45% which represented the transplant pool, had an expansion rate of 13.1%. This model did not make a distinction between the two dialysis modalities: HD and CAPD [3].

2.15 Health care for renal disease in Romania

Romania is one of the former 'communist' countries in Europe lying in the central south-eastern part of the continent. It covers an area of 237,500 km^2, territorially the second largest country in Central Europe after Poland [170; 209, 210, 211] and has had a population of nearly 22 million in the last 25-30 years.

2.15.1 The economic and social environment

Since the post-1990s events, governments have been democratically elected, but arguably, the first real political change took place with the 1996 elections.

The 1996 government declared that progress in the fiscal and monetary policy was an essential precondition for sustainable improvement in the country's microeconomic performance, which also would have an impact on the country's services. The short-term outlook for Romania remained uncertain through the mid-1990s, and constraints in public spending and a firm monetary policy were considered essential.

The ‘centrepiece’ of the 1996 government programme was the legislative package of over 100 laws which was adopted in 1997.

By 1998-1999 the government was becoming unpopular as a result of little or no progress in the economic reforms. Unemployment in men rose from 5.7% in 1996 to 8.5% in 1997 and in women from 7.5% to 9.1%. Unemployment in those aged 15-24 reached 19%.

Table 2.22 summarises how Romania stands in comparison with some of its neighbours at similar stages of development, and some more developed countries.

Table 2.22: Economic and Health Indicators for selected countries 1996-8 and 2007-9

Indicator		*UK*		*US*		*N Z*		*Hungary*		*Poland*		*Romania*	
		F	*M*	*F*	*M*	*F*	*M*	*F*	*M*	*F*	*M*	*F*	*M*
Life expectancy at birth (years)	*1996-8*	79	74	79	73	79	74	75	67	76	68	73	65
	2007-9	82	77	81	76	83	78	78	69	80	71	77	70
Infant mortality rate (/ 1,000 live births)	*1996-8*	6.1		7.8		7.4		10.6		12.3		22.3[1]	
	2007-9	4.8		6.3		5.0		6.8		6.7		14.9	
GDP (US$ PPP)	*1996-8*	21,740		29,326		17,272		4,461		3,509		3,975	
	2007-9	34,619		46,381		26,708		18,567		18,072		11,917	
Unemployment (registered %)	*1996-8*	8.2		5.3		6.1		9.9		12.2		7.6	
	2007-9	7.9		9.7		6.0		11.1		9.0		8.1*	

[1] *17 per thousand live births in 2005*

* April 2010 [212]; ^ IMF 2009

Overall life expectancy has increased in all countries including Romania despite its still high infant mortality rate. GDP per capita (PPP) has improved significantly for Romania and two other former communist countries (Poland and Hungary) [213.] Life expectancy with and without CKD can be measured and is an increasingly important index for service planning as populations age. Life expectancy in non-dialysis CKD has been reported for the first time in a Canadian population and results are comparable for Western societies [214].

2.15.2 Organisation and funding of the health care system

In 1998 the Romanian Health Service had a centralised, hierarchical structure, led from the Ministry of Public Health (MoPH) and its local structures, the Public Health Authorities. The system was 100% tax based until 1998, when a compulsory social health insurance system was introduced, the National Health Insurance Fund (NHIF) thus defining the new National Health Social Insurance System. It meant that healthcare funding has been ring fenced from this funding source as opposed to a share given from revenues obtained via general taxation [12; 14]. There are a few alternative insurance schemes, but beneficiaries must work in specific domains or economic activities: defence, transport etc. Private care is based on a fee basis. RRT is delivered in public facilities.

In the last budget before the insurance system came into existence in 1998 the revenue was 9.74 billion dollars US and expenditure was 12.75 billion, leaving a deficit balance of 3.01 billion. A breakdown is given in Table 2.23 [163]:

Table 2.23: The state accounts for health in 1997, Ministry of Health, Romania

Expenditure (million dollars US)		*%*	*Source*
Total expenditure	970.9	62.5%	State budget*
	137.7	8.9%	Special sickness fund
	36.1	2.3%	"2%"
	295.1	19%	Other sickness fund
	114.1	7.3%	Local funds
RRT**	17		Special funds for drugs

* 66% was received from NHIF (WHO, 2003) ; ** reported figure (1996)

Despite the changes in the health care system from NHS type to insurance type with ring-fenced funding, health care remains "free" for the end-user, with a small minority not contributing with premiums and accesses services paid by the social security.

It was the main third party payer that was changed, from the government to a decentralised body, the National Health Insurance Fund (NHIF). There are now different compulsory contributions (insurance premiums) which are collected via NHIF and almost all of the population is covered by basic services.

Before 1998 an undisclosed variable but small part of general taxation, funded the health services. In 1998, and since, contributions or health premiums were set up as follows: an employers' contribution of 7% before tax, and an employee contribution of another 7% from their individual monthly gross salary. Thus the total premium was 14% of pre-tax income.

The revenue collections ensure an annual health insurance fund. Most local health insurance funds also contribute to a national solidarity fund which allows a more equitable and equal distribution of funding at local level. The contribution to the health insurance fund has grown especially after new general taxation rate was established at a flat 16%; this has allowed improvement in revenue collection for health services [215].

Whether any changes were attributable to the new layout of the third party payer system, or whether they were due to economic developments or both, remains undocumented and is also beyond the scope of this study.

The flow in the financial system was restructured in 1998 and further structural changes to the health care system followed, similar to the ways in which payments are made to providers in countries where insurance systems operate in the health care sector. Some of the changes affected renal services and the national renal replacement therapy programme and annual contracts were put in place.

2.15.3 Other resources

The proportion of health care funds devoted to specialist care varies, but historically has always been over 65%. Also, most of the money, over 75%, is used for salaries [163].

Romania's ageing population and the increase in diabetes, a leading cause of CKD, will continue to pose resource allocation issues amongst competing areas of healthcare, renal services included.

Table 2.24: Health care indicators: cross-country comparisons for 1997, 2002 and 2006 [9;11;216]

		1997					*Various years*
Indicator		*UK*	*USA*	*NZ*	*Hungary*	*Poland*	*Romania*
% of GDP on health	1997	6.9	13.6	7.3	6.7	5	2.8 (1997)
	2002*	7.7	14.6	8.5	7.8	6.1	6.3
*Practising Physicians / 100,000 population** *	1997	186	260	210	308	236	180
	2002	209	240	n/a	320	230	196
	2006	246	240	n/a	304	218	216
Hospital beds per 100, 000 population	1997	-	-	-	800	-	739
	2002	399	330	610	786	-	768
	2006	357	-	-	792	645	675

* 2003 (based on 2002 WHO data); ** 2010 (ECHI Indicators (Public Health/ DG SANCO)

Table 2.24 shows that structurally, Romania reached similar levels in staffing and service use indicators to many other countries with the increase in share of GDP to around 6%. The number of beds per 100,000 population is similar to other central-eastern European countries and double that of the UK despite the similarity in numbers of practising physicians per 100,000 population (which was much higher in Hungary for example in 1997 only to become equal in 2006). By contrast this indicator increased between 1997 and 2006 in the UK [9; 14].

Renal Replacement Therapy (RRT) is dependent on specialist nurses. An indicator could be the number of nurses per 100,000 population, yet this is poorly reported in the ECHI database: in 1997 Hungary and Romania had 495 and 517 nurses per 100,000 population [216].

2.15.4 Problems

In 1999 the Ministry of Health identified a number of problems within the Romanian Health Care System, many of which are common elsewhere. Some were still recorded as problems much later on, in 2010, e.g.: an aging population; health care becoming in general more expensive [217]; "insufficient" funding; low 'morale' for some professionals; inequalities in access to care, especially between regions; historical emphasis on specialist care; surplus of hospital beds and low occupancy rates; poor access to services in rural areas; unclear ownership of health care facilities, poor quality of care, migration of health professionals and loss of human resources, etc.

2.15.5 Reforms

As with many other economic sectors, the health care system went through some changes during 1990 to 1996, but the major changes came from 1996 onwards.

The RRT was directly affected through the adoption of new legislation including that of the transplantation Law (Act) which was passed by parliament. However, the political turnover was most significant. Five ministers were appointed and replaced between 1996 and 2000, three of them in one year, 1998. Thus, changes happened mostly at administrative level: a) in the way the health care system operated: from an NHS type (Beveridge) to a Social Insurance type (Bismarck modified) system and b) down to various administrative policies at regional and local level.

Other changes were: the formulation of National Health Programmes, defined around high priority areas, either from an epidemiological point of view (e.g. notifiable communicable diseases, immunisation, cardio-vascular, cancer) or from a financial point of view, such as renal replacement therapy. On the ground most changes occurred in the way things were working in primary care. After 1998 it became a legal requirement that each individual must register with a GP. Thus GPs became the system's gatekeepers during 1998/1999. In the case of renal care, the GP registration never guaranteed an automatic early referral to a nephrologist. Future RRT requirements have continued to benefit from ad-hoc planning on a historical basis.

2.15.6 The history of services for CKD5

Romania started developing renal replacement therapy for end stage renal failure in the early 1970s with an access protocol and guidance which lasted until 1998. Gradually local policies took over from national policy, the age threshold has been lifted and only defined co-morbidities exclude patients from entering treatment. However, inequalities persist since the more liberal criteria are selectively applied, particularly since the service started to be privatised in 2008 [218].

By the late 1990s there was a network of facilities covering most of the country. This type of service was usually provided in teaching and district hospitals. Continuous ambulatory peritoneal dialysis (CAPD) was only introduced in 1995 for patients with CKD5. However, the main modality of treatment remains hospital haemodialysis (HD). Kidney transplantation is legal in Romania and mainly performed with kidneys from living related donors (82%). However the law stipulates that transplantation can be also done with cadaver kidneys [219]. Two centres perform

living related kidney transplantation (LTx): Cluj or Fundeni Bucharest. Cadaver kidney transplantation has been reported in one centre after the transplantation law passed through parliament (1998)[220].

Fig 2.3 shows the distribution of all renal replacement therapy centres as of 1997. Fig 2.4 shows catchment areas of the adult renal replacement therapy centres as of 1997. A more recent geographical distribution has not been available (2011).

2.15.7 National Health Programmes after 1998

"National Health Programmes" are centrally led from the Ministry of Health and supported financially with NHIF funding.

Keeping these programmes under direct political control allowed for minimum disruption in the delivery of care due to the changes that took place in the third party's payer profile. In 1999 there were more than thirty national programmes on the Ministry of Health's agenda.

The budget for the RRT national programme has remained at about 0.5 to 1% of the public funds available for health care, despite an increase in the number of CKD5 patients receiving RRT. Providers remain reliant on sponsor donations. In 2008 when a third of the patient stock transferred into private RRT some £12.5 million worth of new equipment was purchased via one supplier who increased their Romanian market share by 80% compared with the previous year[9; 10; 216].

Renal replacement therapy for end-stage renal failure is a high- technology, high cost medical speciality. Similar to other countries, Romania buys equipment and consumables such as computerised dialysis machines and equipment, specialised consumables, drugs, on the international open market.

The increasingly demand on resources has put pressure on providers, and the third party payers (the government and health insurance fund) via the public health service.

Romania has a need to further develop these services as they require careful planning, resource allocation and resource deployment, particularly when there are competing demands from other medical specialities for same resources.

As a high-technology, high-cost therapy RRT requires strict budgeting controls and other financial regulatory mechanisms to keep spending under control, particularly if cost-effective pathways of care are not rigorously followed [221].

Romania started developing renal replacement therapy (RRT) for end stage renal failure in a few centres in the 1970s. By the mid 1990s there was a network of facilities covering almost all of the country, mainly in teaching and district hospitals [110; 122;177]. Continuous Ambulatory Peritoneal Dialysis (CAPD) for patients with CKD was introduced in 1995 but the main modality of replacement remains hospital haemodialysis (HD) [222].

Figure 2.3: Distribution of all Renal Replacement Therapy centres by district, Romania, 1997

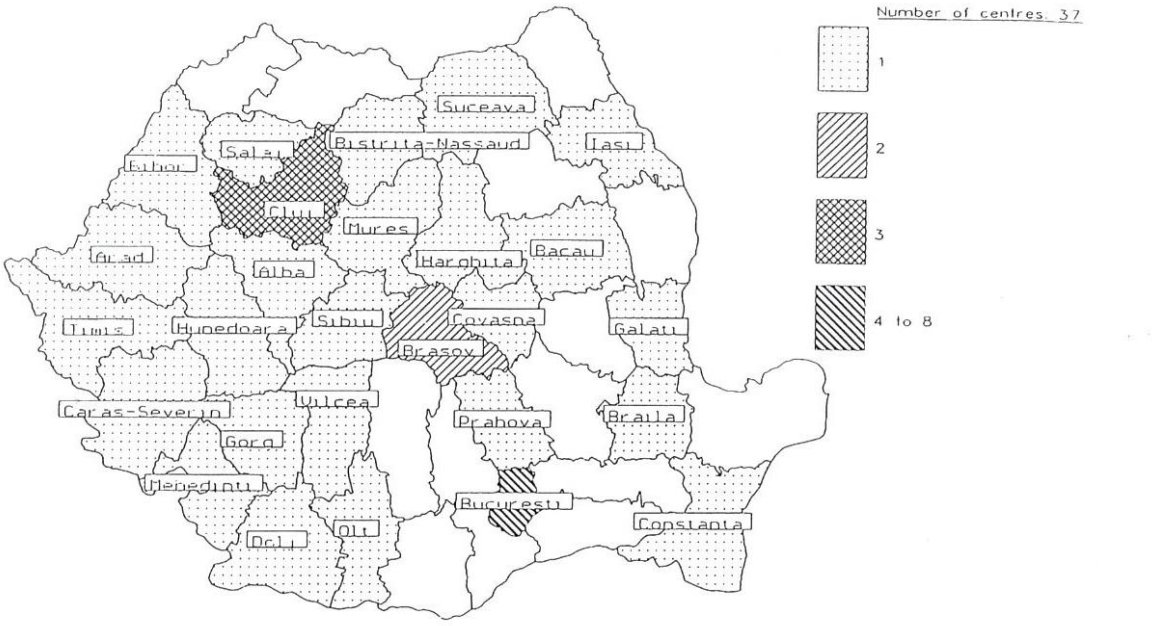
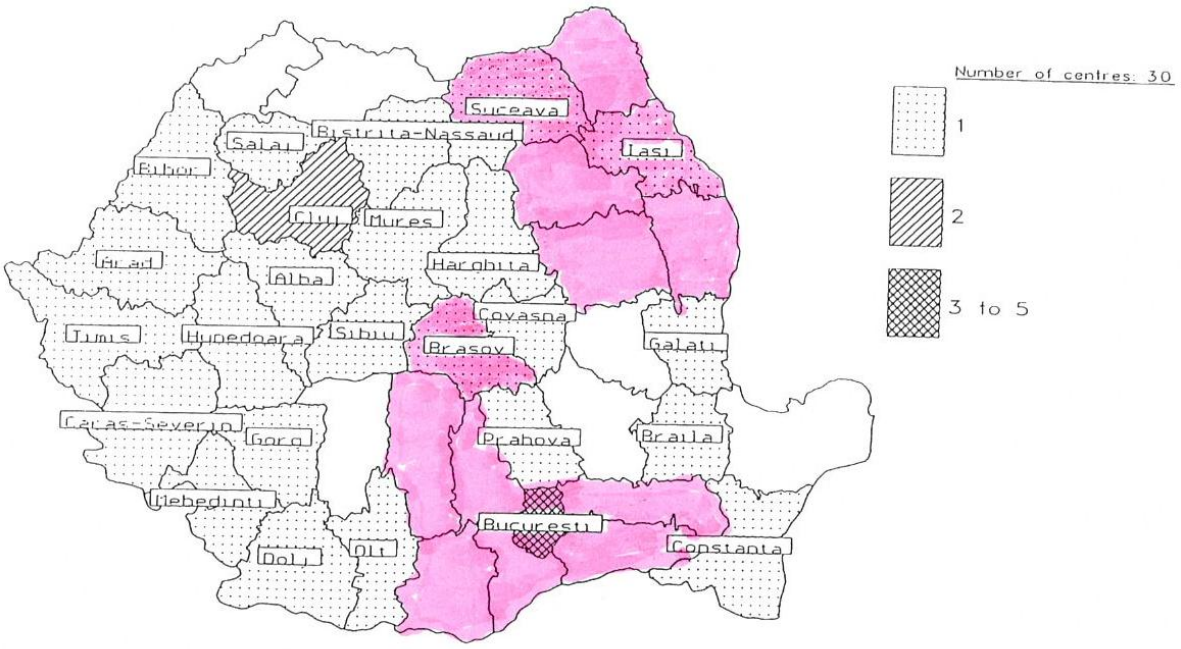


Figure 2.4: Catchment areas of adult renal replacement therapy centres, Romania, 1997



By the mid-1990s two centres started carrying out living related kidney transplantation (LRTx). The number of patients receiving RRT increased from around 1,000 in 1990 to 3,200 at the beginning of 1998 [160; 223,]. The primary and secondary health care systems have yet to develop care pathways for management of the precursors of kidney diseases, renal insufficiency or renal failure.

Service contract negotiation is done annually with the NHIF which sets the budget together with the renal replacement therapy (RRT) national programme and then endorsed by the Ministry of Health. According to the NHIF, by 2009, the budget for the National Programme for CKD5 has increased about five times in real terms in 10 years, closely linked to the increase in the number of patients accepted for treatment. Much of the funding for the increase in the number of dialysis centres and dialysis stations has come from overseas donors.

The Romanian renal replacement therapy market is shared by many known technology suppliers. National sources fund consumables, co-morbidity drugs, patient transport and most administrative services which include all human resources.

Table 2.25 based on data from Cameron for the UK and the US, Ursea and the Ministry of Health for Romania gives preliminary crude comparative figures for 'burden of illness' and health care budgets for the three countries [6;177; 218].

Table 2.25: *Demographic data, morbidity and RRT*

Country	*Population (millions)*	*SDR diseases of circulatory system/ 100,000*	*SDR malignant neoplasms/ 100,000*	*Annual CKD5 on RRT acceptance (pmp)*	*Annual CKD5 RRT stock (pmp)*
USA 1997	280	357.1	214.3	232.8	884.3
USA 2008	298	n/a	n/a	295.2	1,333.5
UK 1996	55.6	449.6	269.8	125.9	449.6
UK 2008	59.7	188.09	177.9	109^	746^
Romania 1996	22.6	195.7	163.2	20.3	58.6
Romania 2008	21.7	558.32	179.8	-	341.1**

* SDR = standardised death rate; n/a = not available; **2007 (reported in absolute number of patients and a rate per million population or pmp was calculated); ^ these indicators are for 2007

Table 2.25 shows crude (1996) and standardised death rates (SDR, 2008) which should be interpreted with care. Countries such as the USA and the UK have seen increases in their populations of 6% and 7% during the eight year interval, while Romania's population has changed little since the 1980s, the most recent estimate being 21.5 million (2008) which represents a small decline. It can be observed from these general indicators that Romania lags behind the UK and the USA in circulatory diseases and renal replacement therapy. In 2008 the Romanian and UK rates for cancer were similar, but the UK rate had gone down by 51% since 1996 while Romania's had increased by 10%. [2; 9; 162; 216]. There was no recent information on SDRs for circulatory diseases and malignant neoplasms in the USA.

2.16 Summary of the literature review

2.16.1 Definitions of chronic kidney disease

Clinical and epidemiological definitions are complementary. Section 2.3 gives the epidemiological definition of stage 5 chronic kidney disease (CKD) or just CKD5 used throughout this research.

2.16.2 Risk factors and precursor conditions

CKD5 develops over years or decades if an individual is exposed to a primary renal condition which becomes chronic. The main primary renal conditions are diabetes and hypertension (raised blood pressure above 140/90 mm Hg). These in turn are related to lifestyle factors, including obesity and smoking. The associations between diabetes and hypertension and renal disease are summarised in Table 2.26.

Table 2.26: Summary of risks associated with chronic kidney disease and CKD5:

Factor or precursor disease	*OR: range for association with CKD*	*OR: range for association withCKD5*
Diabetes mellitus	1.5 to 6.1	7.5 to 9.9
Hypertension	1.1 to 3.1	1.5 to 5.7
Overweight (via DM?)	1.2 to 3.1	1.2 to 1.3
Obesity		3.0
Smoking	1 to 1.6	1.4 to 2.6

- Further points include the following: overweight and obesity are strongly associated with diabetes, with ORs from 3.4 to 8.1. However once on renal replacement therapy, being overweight may be a "protective" factor, giving rise to the term 'reverse epidemiology", phenomenon which is incompletely studied [105,106;155;174; 224];
- obesity is strongly associated with a risk of developing high blood pressure (ORs from 2.80 to 8.60); this points to interaction between risks.
- there does appear to be a link between smoking and diabetes (OR from a meta-analysis of 14 studies 1.44), between smoking and chronic kidney disease, particularly in males and in those aged >40 years, but any link with hypertension is a very weak one (OR is one study 1.1, two studies not significant.)

Other lifestyle or environmental factors may be related to chronic renal failure/ end-stage renal failure directly or, indirectly via diabetes and hypertension.

2.16.3 Disease progression and prognostic factors

The natural history of renal disease is complex since progression due to the underlying disease can very rarely be differentiated from progression due to adaptive factors.

- Factors such as age, underlying condition and presence of co-morbidity have been included in risk classifications of RRT patients, because they are predictive of mortality
- Patients with diabetes and myeloma have an increased risk of death. However survival in patients with diabetic nephropathy is now much improved, firstly through better disease (diabetes) management which delays the development of the nephropathy, and secondly due to progress in transplantation with a simultaneous pancreatic-kidney transplant

2.16.4 Treatment

Renal replacement therapy has two main modalities: dialysis (haemodialyis, haemofiltration, peritoneal dialysis) and transplantation (living donor or cadaver donor).

The literature describes various combinations of approaches to treatment, with some countries relying more on haemodialysis (e.g. USA, Romania, Greece etc) whilst others have shifted towards peritoneal dialysis (e.g. UK, Canada).

Technology has evolved and synthetic membranes plus the use of bicarbonate-buffered dialysate are evidence of best haemodialysis practice; and use of Y-set/ modified Y-set in CAPD represents best known practice for this modality.

2.16.5 Need versus requirement for treatment

Need is measured in different ways: normative need includes expressed need and reflects requirement for RRT; comparative need includes health economics and also elements of equitable distribution of resources.

This research focuses on requirement versus a generic need for treatment or healthcare for CKD5 patients. That is because of the many definitions of need. CKD is also complex, yet staging assists with timing at least some interventions through primary and secondary care at first. Treatment requirement for CKD5 falls into specialist care where planning is required. The assumption here is that once an individual patient reached stage 5 this individual needs a nephrology referral and after closer clinical monitoring (proteinuria and blood pressure) may require RRT. RRT requirement may be delayed through medical treatment.

2.16.6 Outcomes

If a patient is late diagnosed with CKD5 and is not monitored or does not start any treatment, conservative or RRT if needed, the risk of death becomes more imminent. Thus survival is the main outcome studied in RRT. One-year probabilities are over 90% (excluding patients who may die within the first 3 months of treatment, who have a higher mortality; these patients are outside the scope of this study). A 1-year fatality has been reported as around 18-20% overall in the USA [35], but increases with age [92], from 9% in patients aged 20 to 44 to 17% in those 46 to 64 and 24% in those aged 65 and older. Duration of survival is also a key outcome for planning purposes, because this is associated with the prevalence of the condition and thus the number of people requiring RRT. Individual risks and population risks provide different information: for clinicians and decision makers [155; 174].

There is some evidence for misclassification on the death certificates of patients undergoing RRT. Nonetheless a third to a half of deaths is attributed to cardio-vascular causes, a rate usually higher than in the general population and most likely a complication of the renal condition. A further 12-19% is due to infections; and 10-12% is attributed to "unknown cause". Depression was independently associated with a higher risk of mortality among HD patients [110].

Another outcome is quality of life. This has become an important intermediate treatment outcome and is related to its delivery and its quality. There is a vast range of measures, both generic and disease specific to allow measurement of health-related quality of life of patients undergoing renal replacement therapy. For some dimensions of health-related quality of life, transplantation gives similar values to those in the general population. For most dimensions of quality of life, patients on hospital HD or CAPD score lower than the general population or transplanted patients.

2.16.7 Estimating population burden of chronic kidney disease (stages 1 to 5)

There are epidemiological indicators which combine parameters: prevalence of precursors with incidence (acceptance on treatment) and prevalence (stock). The literature is scarce in their application in the case of CKD stages 1 to 5. They were used in this research.

Indicators useful in measuring the burden of chronic kidney disease, described in Chapter 3, are:

The population attributable fraction (proportion), sometimes called population attributable risk percent or PAR% or, the proportion by which the incidence rate of chronic kidney disease could be reduced in the population if a defined exposure were eliminated. The calculation of PAR% helps with benchmarking against the proportion of a precursor in the ESRF or CKD5 on RRT stock (%); and

The impact fraction (IF) which helps with benchmarking against annual acceptance of CKD5 on RRT (incidence pmp) at t2, say after one year, when the prevalence of a precursor changes at t2 (Chapter 3 shows the Methods and Results). Assumptions were made in this research that risk act individually on CKD as the multiplier effect measurement was out of the scope of this research. This is further discussed in the Conclusion.

2.16.8 Economic evaluation and cost-effectiveness studies

Economic evaluations are difficult to carry out, especially for a complex condition such as end-stage renal failure [1]. It should involve the expertise of a multidisciplinary team (economists, physicians, statisticians, health services researchers, managers, etc).

Different countries and settings may give different results. Research should be based on 'standardised' methodologies (e.g. the use of Purchasing Power Parities) in costing methods used for cross-comparison studies or for benchmarking purposes [1;186].

Studying costs in association with treatment outcomes can assist service planners in assessing the cost-effectiveness of renal replacement therapy when there is competition for resources.

Transplantation is the most cost-effective renal replacement therapy method.

2.16.9 Decision support modelling for policy and planning

Models allow decision-makers to explore scenarios and policy options; e.g. CKD5 on renal replacement therapy: modifying the acceptance rate, providing and maintaining a constant transplant rate, the effect on stock of increasing patient survival, changing the numbers of facilities, capacity etc. [60].

Modelling can become an important tool for main stakeholders (providers, consumers and third party payers). This can assist the treatment requirements with better evidence, clearer pathways and can improve efficiency. However, models that are too simple will often fail to capture important aspects of the real world, particularly when economic times are volatile [224].

The complexity of models should only reach that level where health care professionals, policy makers, economists and, last but not least patients, can judge the validity of the reported results from a treatment model. It should not mislead users or patients, budget holders and further research.

Decision-makers need be made aware of the possibility and implications of "uncertainty in key variables". Sensitivity analyses can be important in providing clarification [1; 194;205;208.].

3 Epidemiological modelling of kidney disease in Romania

3.1 Introduction and objectives

The objectives of this chapter are:

- to estimate the current burden of chronic kidney diseases in Romania;
- to estimate the prevalence of, and trends in risk factors and precursors of chronic kidney disease and CKD5 in Romania; and on this basis; and
- to estimate the future burden of CKD5 in Romania:

- Specifically this will involve: selecting plausible scenarios for the future prevalence of diabetes, hypertension and smoking in Romania as the precursors of chronic kidney disease, and of the odds ratios linking these precursors to kidney disease; and
- On the basis of these scenarios, constructing plausible scenarios for the future burden of chronic kidney diseases in Romania.

3.2 Methodology and Methods

3.2.1 Definitions

- *Chronic renal insufficiency due to chronic kidney disease (CRI-CKD);* the loss of kidney function which becomes clinically apparent by stages 3-5 and only detectable through screening in stages 1 and 2; an underlying chronic kidney disease (CKD) is established by stage 3, i.e. the likelihood of those in need of pre-dialysis nephrological care is clinically detectable; the evolution of the functionality of kidneys beyond stage 3 depends on the underlying CKD;
- *Chronic kidney disease* (CKD): those who have reached stages of renal functioning insufficiency but who are not necessarily receiving any nephrological care. This may be either because their condition is still undetected, for which proxy measures are used (e.g. type 2 diabetes and hypertension prevalence and risk of progression towards CKD5 or, because the treatment is not available or accessible (unmet need); and,
- *Chronic kidney disease stage 5* (CKD5) on RRT only: those who have reached the severe stage of chronic renal insufficiency, who require replacement therapy and receive it (in need), whether with dialysis or a kidney transplant [48]. The difficulty with this definition as a basis for

health care needs assessment and planning of RRT services is that it is partly dependent on existing levels of provision and service capacity, thus differentiating between normative and expressed need [21; 122;155;174;177]).

The prevalence of chronic renal insufficiency (CRI) with chronic kidney disease (CKD) in stages 1-5, both point and period, can be estimated using various sources of data [49; 70; 73; 75]. Most of the literature is concerned with stage 5 under treatment (which is also used in this research in the treatment model), but estimates for stages 3-5 can also be made, and were used here in the conceptual epidemiological model (Appendix 2) [65; 96; 115; 225,226].

3.2.2 Sources of data on burden and precursors

3.2.2.1 The Romanian National Health Survey

The 1997 National Health Survey was used as a secondary source. This survey was based on interviews, clinical records, a standard clinical examination, and compulsory screening tests. The sample (n = 9,821) was designed to be representative of the national population aged 15 years or more, and used a stratified (five step) sampling method: region, district, locality, household, and individual [163]. The original dataset for the 1997 survey was obtained. This provided for up to five diagnoses per patient, including a possibility of two primary renal diseases.

Period: Data collection and processing took place during 1997. The 1997 results are presented along with earlier results (1983 and 1989) to show trends.

Validity checks: Validity checks were performed at the source of data entry by staff who prepared the dataset.

3.2.2.2 The Romanian National Renal Registry

This registry provided data on end-stage renal failure and some very limited data on precursors [60; 152; 223]. The latest year for published estimates was 2004. Consistency checks for these figures have been made by comparing them with earlier reported or published estimates [103; 111; 122; 160;177]. The validity and accuracy of reporting may have improved somewhat between 1996 and 2004, but this is uncertain [122; 177; 227].

Period: The main sources of data are Registry reports available for the members of the Romanian Society of Nephrology from 1992 to 1996 [177]; data on later years, such as e.g. 2000, 2001 and 2003, were available through published literature [110,111; 122;227].

Validity checks: Checks were made at the point of data entry. Validity checks for any raw data from this source were not possible. Validity remains highly questionable, and has implications for the interpretation of outcomes, including the validity of the policy scenarios.

3.2.2.3 Other sources of data

In 2006 the MoPH Centre for Health Information, Informatics and Statistics, reporting for the National Health Insurance Fund (NHIF), published updated figures for hypertension and diabetes since the last national health survey in 1997. The most recent figures are for 2003-2005 [216]. The figures reported were much lower than those in the 1997 survey and the prevalence was around 6%. There was no other information, for example related to validity checks or the threshold definitions of hypertension; i.e. whether 140/ 90 mm Hg or 160/90 mm Hg was used in case inclusions.

Neither source (National Renal Registry and National Health Insurance Fund Register) specifies the method of data collection for the conditions leading to chronic renal insufficiency. However, a published report which includes data from 1990s and 2003 show an increase in co-morbidities such as diabetes and hypertension in patients undergoing RRT from 2002 onwards [122; 150;162;216]. One reason for this may be the health insurance default process whereby chronic conditions are now compulsorily monitored for policy and service planning purposes and have therefore become visible at the point of care. The ICD-10 was used for this period (2003- 2005). The rates reported are: prevalence per 100,000 population for hypertension and incident cases as absolute numbers for diabetes [162].

Period: 2003 to 2005.

Validity checks: There is no information available on validity checks and assumption is made that these data were all checked at the point of entry.

3.2.3 Analysis of data on burden and precursors: methods

New variables were created such as body mass index. Tables were produced for prevalence rates of disease and precursors.

Age-specific rates from the 1997 Romanian National Health Survey were applied to data and estimates of local demography to give estimates of local point prevalence of precursor conditions: primary renal diseases, diabetes and hypertension. The population estimates used were from Eurostat [170].

A similar approach was used for estimation of prevalence of CKD, but without a breakdown by age.

Reported point prevalence was estimated for a wider range of disease categories based on ICD-9 coding. This coding was used with the national health survey data. In order to simplify data processing, conditions relevant to this study were re-coded into four major categories: primary renal diseases (all renal conditions), hypertension, diabetes mellitus and chronic renal insufficiency. Survey methods and the diagnostic criteria for each of 99 conditions and disabilities are listed in the main official Survey Report. Definitions of primary renal diseases are given in Appendix 3.

The results of new analyses were checked against the figures in the published reports [122; 148].

Odds ratios (ORs) were computed to estimate the association of primary renal disease, diabetes mellitus and hypertension with chronic kidney disease in univariate analyses.

The Population Attributable Risk percent PAR% (or PAF = population attributable fraction) was used to estimate the proportions of end-stage renal failure and diabetic nephropathy under renal replacement therapy attributable to e.g. diabetes (Section 2.9.2.2). The fraction of chronic kidney disease attributable to e.g. diabetes mellitus or hypertension is difficult to measure directly, but can be estimated indirectly from the ORs (or the Rate Ratios in case of prospective studies) using the Levin formula:

$PAR\% = P_e (RR-1)/ 1+P_e (RR-1)$

This is the proportion or percentage by which the incidence rate in the population would be reduced if the defined exposure were eliminated (P_e= proportion exposed in the population and

OR = rate ratio of incidence of condition). In this case the incidence is for CKD5. Data are very sparse for CKD due to the low observed incidence. This formula assumes other causes have had equal effects on the exposed and unexposed groups and one other assumption that no multiplier effect for multiple hazards was considered [228.]

For example, suppose that diabetes is the "exposure" factor of interest with a prevalence of 4% in the general population, and the incidence rate ratio for diabetic nephropathy in the literature is RR = 12 [56]. Then the calculated PAR% with the two parameters, is interpreted as the proportion by which the incidence rate of end-stage renal failure due to diabetic nephropathy could be reduced if diabetes were to be eliminated as risk factor and in this example this is 30.5%. This was also benchmarked against the existing proportion of diabetic nephropathy on RRT [122; 227].

Prevalence figures for diabetes, hypertension and smoking at baseline (1995), and ORs from the literature linking these precursors to chronic renal disease, were used to estimate PARs% for CKD in 1995. These PARs% were then combined with estimates of prevalence in 2005 and 2015 to provide estimates of the estimated PARs% of chronic kidney disease for these factors in 2005 and 2015. Then, assuming that the number of cases *not* attributable to each precursor remained constant over the period, the prevalence of chronic renal disease in 2005 and 2015 was estimated. This was done for a variety of scenarios for precursor prevalence and ORs (RR was available only for diabetes), and for combinations of precursors.

The Impact fraction (IF) was also calculated in assisting scenarios for low and high acceptance (incidence) at t2 (future moment in time) on RRT [229]. Summation is across the levels of exposure, however considered here dichotomously as: exposed and not exposed under the same assumption that there is no multiplier effect.

The formula is:

Impact Fraction = IF = 1- $\Sigma p2$*RR/ $\Sigma p1$*RR and this can be substituted in the formula below to establish low or high incidence rate ratios and proxies for future estimated acceptance on RRT:

Incid $_2$ ESRF (or Acceptance on RRT) at t2 = Incid$_1$ ESRF at t1 *(1-IF)

In the impact fraction (IF) subscripts 1 and 2 refer to the higher and lower risk level or, the before and after a change (t1 and t2) in the prevalence of precursors. RRs can be replaced with ORs [229].

Both PAR% and the IF help with benchmarking against: 1) proportion in stock (% precursor which led to CKD5, such as in the case of diabetes) and 2) acceptance (incidence of CKD5 at entry point on RRT when prevalence of precursors change from t1 to t2)

The low and high levels of prevalence of precursors and ORs or RRs were used in establishing PAR% as well as the IF. A summary of results is given below in Table 3.12.

Data were analysed with Excel.

3.3 Reanalysis of data from the 1997 National Health Survey

3.3.1 Sample representativeness

The age distribution of the National Health Survey sample was checked for representativeness against the age distribution in the Eurostat population estimates for Romania in 1997. The results are shown in Table 3.1. The 15-24 year-old age- group appears slightly under-represented (16% in the survey vs 19% in the population) while the 55 – 64 and 65- 74 age groups appear somewhat over-represented (32% vs 26%). Forty-six percent (46%) of the sample were male compared to 49% in the population. It was not possible to check whether the urban/rural split in the sample was representative.

Table 3.1: *The Romanian population by age group in 1997: national* and survey sample*

Age group	*Number*		*Proportion (%)*	
	Population	*Survey*	*Population*	*Survey*
<15	n/a	n/a	n/a	n/a
15-24	3,804,979	1,525	22.0	15.5
25-34	3,246,987	1,555	18.8	15.8
35-44	3,188,645	1,699	18.4	17.3
45-54	2,597,509	1,534	15.0	15.6
55-64	2,511,831	1,877	14.5	19.1
65-74	1,932,691	1,301	11.2	13.2
≥ 75	n/a	360	n/a	3.7
All 15+	17,282,642	9,821	100%	100%

* Eurostat reference population.

3.3.2 Prevalence of chronic renal insufficiency

The survey only reported twelve cases of chronic kidney disease. On this limited basis the crude prevalence of chronic renal insufficiency (MDRD with e-GFR <60) was 1,222.5 pmp (per million population) with a very wide 95% confidence interval (631.4 to 2,134.4 pmp). In 10 of the 12 cases at least one criterion cast as "associated precursor condition" was recorded. Five had primary renal disease, 3 had hypertension and one had diabetes mellitus. One had both hypertension and diabetes. Age specific rates are highly unreliable, but are given in Table 3.2.

3.3.3 Prevalence of primary renal disease

A total of 298 diagnoses of primary renal diseases were recorded in 283 individuals, giving a prevalence of 2.9% (95% CI: 2.6 to 3.2%). The official Survey Report gives an overall rate of 2.5%, in broad agreement with the reanalysis.

A primary renal disease was recorded as co-morbidity in only 5 of the 12 cases of chronic renal insufficiency. Of these, there were 3 interstitial nephropathies, 1 nephrotic syndrome and 1 prostatic hypertrophy. The 278 individuals who did not have a recorded diagnosis of chronic renal insufficiency had 294 primary renal diseases diagnoses, some individuals again having more than one. Of these diagnoses, 53% were kidney or uretheral lithisasis, 23% prostatic hypertrophy, 19% chronic interstitial nephropathy, 2.3% chronic glomerulopathy, 1.7% nephritic syndrome and 1% autosomal polycystic kidney disease (ADPKD). No more recent data were available except the proportionate distribution of CKD5 on RRT for 2003 by Mircescu et al [122]. These proportions differ from those from the national health survey as they represent individuals on RRT.

Table 3.2: Distribution by age group of chronic renal insufficiency and main underlying conditions: percentage prevalence rates (Romania, 1997) [162]

Condition	*Sex*	*No. of cases*	*15-24*	*25-34*	*35-44*	*45-54*	*55-64*	*65-74*	*75+*	*Overall rate*
Chronic renal insufficiency	*m*	5			0.14	0.00	0.15	0.50	0.00	0.11
	f	7			0.11	0.23	0.09	0.29	0.50	0.13
Primary Renal Disease	*m*	141	0.4	1.4	1.1	3.4	5.2	7.3	11.3	3.3
	f	142	0.2	1.3	3.7	4.1	2.4	4.0	2.7	2.7
Diabetes	*m*	128	0.3	0.0	0.5	2.9	6.1	7.1	5.7	2.8
	f	135	0.2	0.2	0.7	3.2	5.2	5.6	2.0	2.5
Hypertension	*m*	653	1.1	8.2	10.8	13.9	27.2	22.6	15.5	14.5
	f	796	0.1	3.2	7.7	14.6	31.7	22.9	14.7	14.9
Diabetes & hypertension	*m*	26				0.6	1.0	1.5	0.7	0.58
	f	34				0.3	1.7	1.2	0.6	0.63
Respondents	*m*	*4492*	*724*	*378*	*715*	*794*	*702*	*761*	*413*	
	f	*5329*	*801*	*462*	*794*	*907*	*978*	*897*	*490*	

3.3.4 Prevalence of diabetes mellitus

The reanalysis of the survey data gave 263 individuals coded as having diabetes, a prevalence rate of 2.7% (95% CI 2.4 to 3.0%). The published report quotes 3.2% as the point prevalence for diabetes mellitus in adults aged 15 or more.

Cross-checking against cases with glycaemia >= 120 mg% and other diagnostic criteria for diabetes proved difficult. However, 19 people in the dataset were not coded as having diabetes even though they had an impaired fasting glucose test of ≥ 120mg/dL. Adding these to the coded diabetics increased the rate to 2.9%.

The prevalence rate for 2009 in the EuroDiab study was reported as 4% [161].

3.3.5 Prevalence of hypertension

In the National Health Survey data, hypertension was far the most common of the precursors of kidney disease. The overall prevalence was 14.6% (95% CI of 14.4 to 14.9%). However there was considerable variation in crude specific rates between the 41 Romanian counties, ranging from 2.4% to 17.5%.

Again, cross-checking cases coded as hypertension against their blood pressures proved difficult. A cut-off point of 140/90 mm Hg was chosen for the new analysis in line with the international standard definition of JNC-VIth revision also used by NHANES [53; 78] and HSE [85], which is different from the threshold chosen by the survey methodology in line with WHO MONICA (1997) which uses 160/90 mmHg. The figure in the official Survey Report was 16.7%, a difference of 2.1% that could be explained by different cut off thresholds.

However, in 2006 the National Health Insurance Fund provided overall prevalence figures for hypertension in the region of 6%, making the different estimates of the prevalence of hypertension highly variable [216]. However, these could be registered patients who are in treatment.

3.3.6 Prevalence of diabetes and hypertension together

Data on the prevalence of diabetes and hypertension together are given in Table 3.2. If the prevalence of diabetes and hypertension together is estimated as the product of the prevalence of diabetes (with or without hypertension) and the prevalence of hypertension (with or without diabetes) the total estimated number of cases in the survey come to 32 for males and 34 for females, compared to actual figures in the survey of 26 and 34. This suggests that estimation of the numbers with hypertension and diabetes combined on the basis that the two conditions are uncorrelated could be an acceptable approach.

There are no comparative figures in the national report for 1997, or for 2007.

3.3.7 Trends in prevalence

Results from the last three national health surveys (in 1983, 1989 and 1997), which used identical methods, are summarised in Table 3.3, by year of survey, condition, sex and residence. The official reports suggest that the three surveys were representative to similar extents. Comparing the 1997 results with the two previous surveys (1989 and 1983), the 1997 Survey Report concluded that:

"The prevalence of primary renal diseases as defined in Chapter 2 (PRD) has almost doubled in 1997 compared with the 1989 estimate with an increase of 83%, and trebled if compared with the 1983 estimate; there was an increase of 56% from 1983 to 1989; in urban areas the increase from 1989 to 1997 was only of 66% whilst in the rural areas the increase was more than double." [34; 179].

Table 3.3: Trends in prevalence of CKD, hypertension and diabetes, Romania, National Health Survey for 1983, 1989 and 1997

	Year	Prevalence rate (per 100 population surveyed age 15+)							
		Total	Increase	Male	Increase	Female	Increase	Urban	Rural
Primary Renal Disease	1983	0.88		-		-		-	-
	1989	1.38	*56.8%*	1.09		1.61		1.84	0.88
	1997	2.53	*83.3%*	2.07	*89.9%*	2.93	*82.0%*	3.06	1.97
Diabetes [b]	1989	2.69		2.44		2.88		3.55	1.83
	1997	3.18	*18.2%*	3.41	*39.8%*	2.98	*3.5%*	3.81	2.48
Hyper-tension [a]	1989	15.6		14.2		16.7		15.2	15.9
	1997	16.7	*7.1%*	14.8	*4.2%*	18.4	*10.2%*	17.2	16.1

Source: MoH, Romania [179]

There are no data from 2007/08 suitable for inclusion in this table.

The prevalence of diabetes mellitus increased by 18% between 1989 and 1997. It increased by 40% in males but only 5% in females. Also it increased significantly more in rural areas, by 36% compared to 7% in urban areas. There was a further increase from 2.9% to 4% (37%) between 1997 and 2007, but there was no available breakdown by age or gender.

3.3.8 Association between different risk factors and kidney disease in the survey data

Table 3.4 shows the strength of the associations found in the National Survey data between different risk factors and chronic renal insufficiency, in terms of odds ratios (ORs). Two cut-off points were chosen: BMI=25 for overweight and BMI= 30 for obesity.

It can be seen that the ORs linking overweight and obesity to CRI are low. There is some evidence from the literature that while BMI is a risk factor for the development of end-stage renal failure, once renal disease has developed, overweight appears to be protective ('reverse epidemiology' [131,132]), which may account for this lack of association. Nonetheless a variety of studies have shown that high body mass index is predictive of the development of kidney disease.

Table 3.4 shows the links between overweight/obesity, and other risk factors for chronic kidney disease.

Table 3.4 Strength of association between hypertension, diabetes, overweight and obesity data from the national health survey, Romania, 1997 for precursors of diabetes and/ or hypertension[1]: Obesity[2] data

Overweight/ obese: BMI ≥ 25		*Number of cases* *BMI<25*	*BMI≥25*	*OR*	*95% CI*	*p>chi²*
Age ≥ 45	No	2,055	310	0.15	0.14 to 0.18	0.000
	Yes	3,763	3,693			
Age ≥ 50	No	3,906	1,674	2.84	2.62 to 3.09	0.000
	Yes	1,912	2,329			
Hypertension	No	5,192	3,180	2.15	1.92 to 2.40	0.000
	Yes	626	823			
Diabetes	No	5,713	3,845	2.24	1.74 to 2.87	0.000
	Yes	105	158			
Hypertension and diabetes	No	5,778	3,928	2.76	1.88 to 4.06	0.000
	Yes	40	75			
Obese: BMI ≥ 30		*Number of cases* *BMI<30*	*BMI≥30*	*OR*	*95% CI*	*p>chi²*
Age ≥ 45	No	2,322	43	7.92	5.82 to 10.79	0.000
	Yes	6,502	954			
Age ≥ 50	No	5,265	315	3.20	2.78 to 3.69	0.000
	Yes	3,559	682			
Hypertension	No	7,626	746	2.14	1.83 to 2.50	0.000
	Yes	1,198	251			
Diabetes	No	8,618	940	2.54	1.88 to 3.43	0.000
	Yes	206	57			
Hypertension and diabetes	No	8,741	965	3.49	2.31 to 5.28	0.000
	Yes	83	32			

Note for table 3.4: [1] HT defined as 140/90 mm Hg

[2] Obesity is defined in the national health survey as "excess of weight" and compared with tabulated values calculated with the formula: G=T-100-(T-150/4) where G= weight; T= height; 20% or more in G (weight) compared with the theoretical value qualified the person as obese; according to this formula, prevalence was 7.3% in the 15 years and above sample;

Given that height and weight were recorded in the dataset, BMI was calculated according to the formula weight/ height^2 (Quetelet index) and the threshold of 30 was used to define obesity; prevalence was 10.2% in 15 years and above for sample n=9,821; weight and height measurements did not indicate whether self-reported or actually measured or whether scales for weight measurement were similarly calibrated etc. (validity)

3.4 Data on precursors from the National Renal Registry

The Registry does not record information on co-morbidity for conditions leading to chronic kidney disease and end-stage renal failure. Moreover the proportion of patients with underlying co-morbidity showed that in 1991 nearly all end-stage renal failure patients under renal replacement therapy had a primary renal disease. In the 1996 report only 2% were reported as diabetics, and none had hypertension. By 2003 the Registry reported that the proportion of diabetic cases had increased to 10% of all patients on renal replacement therapy from 1% before 1996. The Registry did not provide data by age-group for either 1996 or 2003.

3.5 Estimating the future population burden of chronic kidney disease

3.5.1 Projected changes in population size and structure

The future burden of chronic kidney disease will clearly be affected by the size of the population and its structure. Tables 3.5 and 3.6 show that according to the mid-projections, the population is expected to decline by about 10% for men and 14% for women by 2020. However the proportion of people aged 65 or more will increase by almost 50% (men) and 42% (women) and of those aged 75 or more by over 70% (men) and 56% (women).

Eurostat also provides upper and lower variants on these estimates. For example, according to the upper estimate the population will have declined by 8% instead of 11.5%; according to the lower estimate it will have declined by 15%.

The age-specific prevalence rates of chronic kidney disease and its precursors can be applied to these figures to give projected prevalence rates on the very conservative assumption that the age-specific rates will remain unchanged. The results of doing this are shown in Table 3.7. It can be seen that in spite of a decline in population of more than 10%, primary renal disease would be projected to increase by 18% for men and 9% for women, diabetes by 14% and 8%, and hypertension by 16% and 11%.

Table 3.5: Population estimates for men: Romania, 1995 to 2020 (000s)[170]

Age	*1995*	*2000*	*2005*	*2100*	*2015*	*Change*
0-14	2273	1992	1649	1554	1467	-39.4%
15-24	1855	1732	1617	1397	1094	-44.4%
25-34	1560	1744	1737	1642	1541	-14.2%
35-44	1636	1414	1473	1674	1678	-2.6%
45-54	1277	1477	1556	1352	1421	27.2%
55-64	1370	1225	1179	1379	1462	-6.8%
65-74	1061	1117	1147	1036	1019	13.7%
75+	523	623	731	835	926	72.7%
Total	11555	11324	11089	10869	10608	-10.4%
15+	9282	9332	9440	9315	9141	-3.3%
% 0-24	35.7%	32.9%	29.5%	27.2%	24.1%	-34.9%
% 25-44	27.7%	27.9%	28.9%	30.5%	30.3%	2.4%
% 45-64	22.9%	23.9%	24.7%	25.1%	27.2%	22.3%
% 65+	13.7%	15.4%	16.9%	17.2%	18.3%	48.6%

Table 3.6: Population estimates for women: Romania, 1995 to 2020 (000s) [170]

Age	*1995*	*2000*	*2005*	*2010*	*2015*	*Change*
0-14	2373	2086	1740	1642	1553	-38.5%
15-24	1929	1808	1684	1459	1153	-43.5%
25-34	1606	1797	1801	1709	1600	-13.1%
35-44	1635	1412	1489	1698	1719	0.5%
45-54	1231	1411	1479	1292	1388	29.9%
55-64	1216	1060	1030	1206	1280	-6.9%
65-74	823	868	866	767	768	11.4%
75+	313	373	450	503	528	56.2%
Total	11126	10815	10539	10276	9989	-12.6%
15+	8753	8729	8799	8634	8436	-5.6%
% 0-24	38.7%	36.0%	32.5%	30.2%	27.1%	-32.2%
% 25-44	29.1%	29.7%	31.2%	33.2%	33.2%	7.3%
% 45-64	22.0%	22.8%	23.8%	24.3%	26.7%	27.7%
% 65+	10.2%	11.5%	12.5%	12.4%	13.0%	41.6%

Table 3.7: Projected change in prevalence with constant age/sex prevalence rates, Romania, 1995 to 2020 (000s)

		Primary Renal Disease		*Diabetes*		*Hypertension*	
Men	*1995*	298,466		239,490		285,681	
	2000	312,756	4.8%	244,642	2.2%	1,325,504	3.1%
	2005	327,535	9.7%	252,363	5.4%	1,383,920	7.6%
	2010	334,649	12.1%	257,039	7.3%	1,420,742	10.5%
	2015	347,771	16.5%	267,194	11.6%	1,475,720	14.8%
Women	*1995*	206,257		173,487		1,044,746	
	2000	207,303	0.5%	173,434	0.0%	1,049,242	0.4%
	2005	214,023	3.8%	175,777	1.3%	1,083,133	3.7%
	2010	214,138	3.8%	175,290	1.0%	1,108,487	6.1%
	2015	219,313	6.3%	182,083	5.0%	1,153,452	10.4%

3.5.2 Projected changes in prevalence rates

In the previous section it was assumed that while the demographic structure was expected to change, the age/sex-specific prevalence rates would remain constant. However there is good evidence from other countries (Chapter 2), and some evidence from Romania, that the prevalence of some risk factors is changing. In England, age-specific prevalence rates for diabetes approximately doubled between 1994 and 2006, but are still below rates from the US. Hypertension has been increasing slowly in the US but decreasing in England. Smoking has been gradually declining in both the US and England, but in both cases the declines have flattened out. Obesity and overweight have been increasing strongly and are still increasing in the UK, although they do seem to have peaked in the US.

The second approach to estimating the future prevalence of kidney disease in Romania is based on estimating the impact on the prevalence of chronic renal disease of possible changes in the prevalence of risk factors and precursors.

The precursors considered up to this point include diabetes, hypertension, smoking and obesity. There is some controversy over whether there is a direct link between obesity and kidney disease. However, the link between obesity and diabetes is relatively clear. Thus, including both obesity and diabetes as independent factors in this estimation procedure, risks would double count. For this exercise only the effects of diabetes, hypertension and smoking will be considered.

The next step is to define plausible scenarios for risk factor or precursor prevalence for CKD5 in Romania for the period up to 2016. From Table 2.14 and Table 3.2 it can be seen that prevalence rates for *diabetes* for England in 1994 and Romania in 1997 were reasonably similar for both men at around 2.5-3% and women at 2-2.5%. The English rate for 2003 (about 4%) was similar to the EuroDiab Romanian rate reported in 2009 in the adult population aged 15 years and above. However US rates rose from about 5% in 1990 to over 6% in 2002 and rose above 7% by 2009. On this basis the proposed scenarios for the prevalence of diabetes in Romania are 2.5% (unchanged) and 4% in 2005, and 2.5%, 4% and 6% in 2015 (Table 3.8).

Estimates of the prevalence of *hypertension* in Romania vary widely. The MONICA study reported a prevalence of about 4.7% for 1997, and the Romanian Ministry of Public Health reported a value of 6.5% for 2006 (section 2.12.2). However the analysis of the Romanian Health Survey for the same year gave values of around 14.5% (section 3.2.5), and this is closer to figures from western countries such as the US and UK, which are around 30%. The differences in figures could be explained by misclassification of cases. On this basis the proposed scenarios will be 5% and 14.5% as baselines in 1995; 5%, 14.5% and 27% in 2005; and 5% 14.5% and 27% in 2015.

The prevalence of *smoking* has been high in Romanian men (around 41%) compared with data from the UK and the USA but lower in women (around 25%; Table 2.19). Although the rates are very different in men and women, for the purposes of this analysis an overall baseline figure of 33% will be assumed. The proposed scenarios for Romania will be 33% (unchanged) and 23.5% in 2005; and 33% and 23.5% in 2015.

Table 3.8: Scenarios for projected levels of risk factors in Romania in 2005 and 2015

Prevalence scenarios	*Scenario*	*Source*		*1995*	*2005*	*2015*
Diabetes	Static	Romania	1997	2.5%	2.5%	2.5%
	Mid	England	2003		4.0%	4.0%
	Upper	US	2002			6.0%
Hypertension	static 1	Romania	1997a	5.0%	5.0%	5.0%
	static 2	Romania	1997b	14.5%	14.5%	14.5%
	Upper	England	2003		27.0%	27.0%
Smoking	Static	Romania	2003	33.0%	33.0%	33.0%
	Lower	England	2004		23.5%	23.5%

3.5.3 Impact of trends in precursors on burden of end-stage renal failure

The task here is to estimate the impact on the prevalence of chronic renal disease in 2006 and 2016 of the risk factors/precursors scenarios set out in Table 3.9. As set out in the Methods above, the approach is to estimate PARs% for diabetes, hypertension and smoking for 1995, 2005 and 2015 using RR and ORs from the literature and the different prevalence scenarios, low, medium and high, in Table 3.8. Then, assuming that the number of cases *not* attributable to each precursor remained constant over the period, the prevalence of chronic renal disease in 2006 and 2016 can be estimated.

The literature (Chapter 2) and the analysis of the Romanian Health Survey (Table 3.4) report a range of values for the ORs so a set of scenarios with a plausible range for each OR was set up. These ORs are: for diabetes 7, 9 and 12 as the lower, mid and high variants respectively; for hypertension: 1, 2 and 3; and for smoking: 1, 1.5 and 2.

Table 3.9: Population attributable fractions derived from prevalence of precursors of chronic kidney disease and OR scenarios (Levin's formula)

Year		*1995*			*2005*			*2015*		
		PAR			*PAR*			*PAR*		
		estimate of OR			*estimate of OR*			*estimate of OR*		
	prevalence	*Low*	*mid*	*high*	*low*	*Mid*	*high*	*low*	*mid*	*high*
Diabetes	static	13%	17%	22%	13%	17%	22%	13%	17%	22%
	mid				19%	24%	31%	19%	24%	31%
	upper							26%	32%	40%
Hypertension	static	0%	5%	9%	0%	5%	9%	0%	5%	9%
	static				0%	13%	22%	0%	13%	22%
	upper							0%	21%	35%
Smoking	static	0%	14%	25%	0%	14%	25%	0%	14%	25%
	lower				0%	11%	19%	0%	11%	19%

Table 3.10: Impact of changes in risk factors (precursor conditions) on prevalence of CKD

		2005			*2015*		
		Impact on prevalence Estimate of OR			*Impact on prevalence Estimate of OR*		
		Low	*mid*	*high*	*low*	*Mid*	*high*
Diabetes (D)	Static	100%	100%	100%	100%	100%	100%
	Mid	108%	110%	113%	108%	110%	113%
	Upper				118%	123%	130%
Hypertension (H)	static 1	100%	100%	100%	100%	100%	100%
	static 2	100%	109%	117%	100%	109%	117%
	Upper				100%	121%	140%
Smoking (S)	Static	100%	100%	100%	100%	100%	100%
	Lower	100%	96%	93%	100%	96%	93%
D + H	both static	100%	100%	100%	100%	100%	100%
	both mid	108%	120%	132%	108%	120%	132%
	both upper				118%	149%	182%
D + H + S	all static	100%	100%	100%	100%	100%	100%
	D & H mid, S lower	108%	115%	123%	108%	115%	123%
	D & H upper, S lower				118%	143%	169%

Table 3.10 suggests the following:

- The different estimates of the increase in the prevalence of diabetes could mean increases in the prevalence ratios of chronic kidney disease (CKD) of between 0% and 30% (from 100% to maximum 130%)
- The different estimates of the increase in the prevalence of hypertension could mean increases in the prevalence of chronic kidney disease of between 0% and 40% (from 100% to 140%).
- The different estimates of the decrease in the prevalence of smoking could mean decreases in the prevalence of chronic kidney disease of between 0% and 7% (from 100% to 93%).
- The combined increases in the prevalence of diabetes and hypertension could mean increases in the prevalence of chronic kidney disease of between 0% and 82% if the changes in smoking are zero or can be are ignored
- The combined changes in the prevalence of diabetes, hypertension and smoking could mean increases in the prevalence of chronic kidney disease of between 0% and 70%.

Table 3.11: Impact Fraction: impact of changing risk factors (precursor conditions) on acceptance rates (stage 5 CKD with ESRF and Acceptance at t2)

	Prevalence of risk factor at t2 (t1)	*Acceptance on RRT*	*30-44*	*45-64*
Diabetes	6%	low	10.5	30
	(from 4%)	high	54	105
	4%	low	11.2	32
	(from 2.5%)	high	57.6	112
	6%	low	16.8	48
	(from 2.5%)	high	86.4	168
Hypertension	27%	low	140.4	513
	(from 5%)	high	286.2	982.8
	14.50%	low	75.4	275.5
	(from 5%)	high	153.7	527.8
	27%	low	48.36	176.7
	(from14.5%)	high	98.58	338.52
Smoking	23.5%	low	7.54	27.55
	(from 33%)	high	15.37	52.78

Table 3.11 suggests the following: the incidence of CKD5 can vary not only with a given prevalence of a risk factor, but also with the level of that change, for example in the case of diabetes when prevalence takes values from 2.5% to 4% or to 6% or from 4% to 6%. As an example, the low and high Acceptance rates at t1 were taken from this study, as reported from 16 RRT centres: 20 (lowest) and 80 (highest) pmp. In case of diabetic nephropathy, its Acceptance at t2 can take a range of values between 10.5 and 54 pmp in 30 to 44 year olds and 30 pmp to 105 pmp in the 45-64 year olds when 20 and 80 pmp are used for Acceptance at t1. Because of assumptions made, such as: 1. the prevalence of the risk factor (diabetes) is highest at 6% at t2 in the overall population; and 2. the differences in the occurrence according to age can explain the different levels of Acceptance at t2; it means that Acceptance rates at t2 can take as many values

as: the type of precursor condition, its prevalence in the age group, assuming further that no interaction (multiplier effect) exists between precursors in this example [228].

In the case of hypertension highest value could be 983 pmp and in the case of smoking acceptance can reach 28 pmp from 53 pmp if the prevalence of smoking decreases from 33% to 23.5%. A value of 983 pmp in a maximum 1,940 pmp projected stock could reflect a 50% proportion of RRT due to hypertension, in a given year, assuming all other parameters are kept at values described in the treatment model (Chapter 8).

These incidence (acceptance) rates were used as guidance in the treatment scenarios where acceptance is increased by up to 50% in 10 years, with or without changes in the ratio diabetic/ non-diabetic CKD5 (Chapter 4 and Chapter 8 Tables 8.1, 8.2 and 8.3). The baseline acceptance is between 11 (low) and 85 (high) pmp and has local variations (Chapter 4).

3.6 Strengths and limitations

The strengths of the results obtained in this Chapter for specific objective 1 of this research are:

- Availability of local, national data and information with some precision and accuracy
- Sufficient demographic detail: place of residence, gender, age
- Representativeness of sample at national level
- Comparative trend with two previous cross-sectional point estimates
- Major condition precursors included as well as PRD (primary renal disease) diagnoses

However, limitations are as follows:

- Information or data from a follow-up design are not available;
- It was impossible to validate the data (no random sample with record checks);
- Prevalence estimates (rates) for hypertension were calculated from the National Health Survey 1997 dataset using 140 and 90 mmHg as the threshold. The resulting prevalence (16.5%) was very different from the prevalence given in the published report (4.5%. One possible explanation is that different thresholds were used, such as 160 and 90 mmHg, or that the published report relied on clinical diagnoses with unspecified criteria;

- Overall quality of data could not be established with precision and accuracy (same example as above);
- Many assumptions had to be made in order to estimate PAR%.

3.7 Summary

- Estimates of the point prevalence of chronic renal insufficiency and other major leading causes of chronic renal insufficiency are important starting points for service planning and resource allocation [60,61;88,89]
- The 1997 Romanian national health survey estimates for underlying conditions of chronic kidney disease and chronic renal insufficiency were: main primary renal diseases 2.7% and 3.1%, diabetes 2.5% and 2.9% and hypertension 16.7% and 14.7% with little or no difference between genders, although with substantial apparent geographical variation;
- Not all primary renal diseases contribute to progression to chronic kidney disease and/or chronic renal insufficiency. However, the proportion of patients on treatment with a primary renal disease and other non-diabetic conditions remains high in Romania: 90% as suggested by 2003 data[122].
- The survey showed an age gradient for these conditions: the prevalence of primary renal diseases doubled from the age of 40 years in women and was highest in the over 70 year age-group in men. Diabetes peaks in both men and women after the age of 50 years, with nearly a fourfold increase.
- This study has found that a combination of hypertension and diabetes may increase the odds of developing chronic renal insufficiency development by almost 8 times (OR = 7.74, CI95% from 0.99 to 60.38, Table 5.3). This is in line with the wider literature which has identified an association even for single conditions such as diabetes, with an RR of 12 in a longitudinal study [82]. The caveats here are the cross sectional nature of these data and the small sample.
- The chronic renal insufficiency national estimate of all stages, 1-5, may lie in the region of 1,222.5 pmp in 1997. However, this figure is unreliable due to the very small number of individuals in the survey. The 95% CI, from 600 to 2000 pmp, is very wide. Given this rate, the country as a whole would have expected a total number of affected individuals in stages

1-5 of CRI in the range of n=21,000 (95% CI of 11,000 to 37,000). As around 3,200 patients were receiving RRT at the time this represented an age 15+ specific stock rate of 186 pmp. One reported figure at the time (1997) was 78 pmp and this research found stock rates of up to 230 pmp for the same year [160;177.] This is further discussed in Chapter 9.

- The PAR% for chronic kidney disease entities can be indirectly estimated for various precursors in order to compare the proportion of patients on renal replacement therapy recorded for those with defined co-morbidity where the co-morbidity constitutes an associated "risk" factor; e.g. the diabetes prevalence and the rate ratio of presence over absence of diabetic nephropathy may indicate that if diabetes were eliminated as precursor condition, so would the theoretical proportion of 30.5% of diabetic nephropathy on RRT. The last (2003) renal replacement therapy reported proportion for Romania is about 10%. This difference, between the theoretical proportion, which is a value closer to proportions of diabetic nephropathies in Western societies and the reported proportion could be explained by a series of facts: that not all diabetic cases require RRT as they may be in various stages from 1 to 5, that not all diabetic nephropathy cases in stages 4 and 5 come to the attention of the nephrologist or, that they come to RRT too late, with further consequences in the administrative data, such as, deaths under 90-days on RRT. Patients entering dialysis and not surviving 90 days on treatment are excluded from CKD5 data.

4 Provision of services for CKD5

4.1 Objectives

- to describe the existing provision of services for CKD5
- to assist with the conception of the treatment model: CKD5 under RRT;
- to place and discuss results in relation to the treatment model in international context

4.2 Methodology and Methods

To describe the existing provision of services for CKD5

4.2.1 Sources of data on provision

4.2.1.1 The ERA-EDTA database

The Registry of the EDTA/ERA was contacted in 1997 and the electronic dataset on Romania was re-analysed for acceptance and stock (Appendix 3).

4.2.1.2 A questionnaire for each RRT centre

A Centre Questionnaire was designed to obtain operational and administrative data from all Romanian centres offering treatment for CKD5 (Appendix 4). This questionnaire was sent to all 30 adult renal replacement therapy centres identified through the National Renal Registry. Paediatric units were excluded. The main items in the questionnaire were:

- Year in which the centre was set up

For acceptance and stock:

- Acceptance (new patients) and stock (old and new) per year for 1995 to 1997
- 1997 stock : patients distribution by 5-year age bands
- 1997 stock : patients distribution by renal replacement therapy modality

For resources matching existing provision with renal replacement therapy:

- HD stations : total number and percentage functional; type of station
- HD- types of membrane used
- HD dialysate buffer used
- CAPD activity

- Human resources: full-time dedicated and shared - physicians, nurses, ancillary, others.
- Centre's catchment area
- 1997 financial year Budget
- 1997 financial year Expenditure (Actual Budget)
- Membership of the European Renal Association and year of membership (for cross-check with EDTA 1997 data)

The questionnaire (in Romanian) was sent by post. After receipt of the first three replies, the remaining units were reminded first by telephone and then again by e-mail. In total 16 centres replied out of 30.

Data from 13 centres were usable; these centres replied to the questionnaire in full. Two of the 16 were excluded partly because they opened during 1997, but mainly because there was a problem with misclassification of their patients (i.e. stock patients who moved back to the catchment area as a result of the centre's opening were defined as 'accepted' patients in newly opened centre). A third centre was excluded because it had no defined catchment area and treated diabetic nephropathy only.

Centres have defined catchment areas. Cross boundary flows were considered but turned out to be negligible.

4.2.1.3 The National Registry Report

This secondary source of data was used to cross check the information obtained from the EDTA and the Centre Questionnaire, particularly on acceptance and stock. The validity and accuracy of this source may have improved somewhat between 1996 and 2004, but this is uncertain [122; 227].

4.1.1 *Analysis of data on provision*

4.3.1.1 The capture-recapture method for estimating 'stock' levels

Where data are known to be incomplete but there are independent sources, capture-recapture is a method of improving estimates can be combining data from the different sources. The independent data sources in this case were the ERA-EDTA data for 1997, and the Centre Questionnaire described above. The total number of cases was estimated by the reverse of the process for computing an expected value in the contingency table (Table 4.1) below [229]:

Table 4.1 Capture-recapture method

	Source B	
Source A	Detected	Not detected
Detected	A	B
Not detected	C	

a is the number identified by both sources and b and c are the numbers identified by one of the independent sources not by the other. This gives:

Maximum Likelihood Estimate (MLE): (a+b)(a+c)/a

Nearly Unbiased Estimate (NUE): [(a+b+1)(a+c+1)/(a+1)]-1

A 95% confidence interval can be calculated from

Var (NUE) = $(a+b+1)(a+c+1)(b)(c)/(a+1)^2 (a+2)$.

The proportions of identified numbers are (percentage):

Source A = (a+b)/NUE* 100

Source B = (a+c)/NUE* 100

Sources A, B = (b+c)/NUE* 100

The two sources of data were consulted independently. The independence of the sources could not be fully checked. Assuming that the same responsible data management individual would have reported data to both ERA-EDTA and the CQ was taken into account. The time sequence for the 1997 data was: January 1999 for the CQ returns and June 1999 for ERA-EDTA information returns. Data validation was performed in 3 sampled units starting from the CQ information (Chapter 5).

4.4 Results

4.4.1 Responses to the EDTA survey and the Centre Questionnaire

There were 34 RRT Romanian centres registered with the EDTA-ERA in 1997: 30 adult units, three paediatric units and one providing treatment for acute renal failure (ARF). Of these, 24 (71%) responded to the EDTA survey centres); these were 20 out of the 30 adult centres.

For the Centre Questionnaire, 16 of the 30 adult centres replied. However, only 13 provided usable patient data. Of these, two were set up in 1990 and the remaining 11 in 1994. Neither early established centre (i.e. before 1994) replied to the Centre Questionnaire.

Six centres reported both to the EDTA Register and returned a centre questionnaire. These were six of the more established centres: Iasi, Craiova, Fundeni Bucuresti (Nephrology), Brasov, Oradea and Hunedoara. (Two of these centres, Iasi and Brasov, were among the three units sampled to provide data on patients outcomes): one centre (Iasi) which responded to both EDTA survey and Centre Questionnaire had in 1998 the largest catchment area (six counties with a population of over 3 million).

4.4.2 Data from the EDTA and the Centre Questionnaire

From the six centres with data from both sources, the modal distribution was: 82% on HD, 13% on CAPD and 5% transplants. This confirms that HD as the dominant modality, with CAPD second and [living related] transplantation third. Table 4.1 gives further information from these two sources and the non-respondent estimates are the result of the identification of non-respondent centres, plus the total number of patients treated in 1997 as reported by the National Registry. The non-respondent estimates are unreliable and the imbalance patients in these centres could be explained by the very small numbers of patients treated in these centres.

The two sources provided independent figures for 1997, which made the capture-recapture method (CRM) possible.

4.4.3 Data from the National Registry

Estimates from the Centre Questionnaire and EDTA-ERA were compared with the national registry reported stock estimate for 1998 for triangulation. One reported 1997 figure was that of 3,189 patients (185 pmp), of which 912 were newly accepted during the same year [160]. For

comparison, for 1994 the reported stock rate was 55 pmp [177] and in 2003, the reported stock was 7,026 (250 pmp) of which 2,790 were newly accepted during the same year [122].

Subtracting the 912 (acceptance), from 3,189 (stock), the result became 2,277. The national figure reported in the National Registry Annual Report for 1997 and preceding the 2000 publication was 2,474 patients. Part of this difference, between 2,277 and 2,474 may be attributable to paediatric patients (<15 years of age) and also other reasons, such as double counting, or simply by having newly accepted patients included in stock. However, the difference is small [160; 227] .

4.4.4 The stock of patients

The importance of classification of conditions and modalities of treatments was explored and discussed in Chapter 2. Because the reported figures are unreliable or incomplete, the stock was estimated with using the capture-recapture method (CRM) (Section 4.4.6) [229].

4.4.5 Acceptance for RRT

The Registry records only patients with CKD5 on RRT. This secondary source of data provided information on acceptance, reporting it as the "incidence benchmark" of CKD5 (that of treatment requirement). In 1995 the reported estimate was 127 new cases per million population (pmp) and in 2004, despite a major expansion of services, it remained at a reported 128 pmp. The basis for these estimates is, however, obscure despite the fact that they were both reported as national figures. The 2003 figure may have been the caseload from 71 centres reported for Romania, but it was not possible to confirm this [122].

A similar acceptance rate of 128 pmp was found for Austria in 1999. At the time, the explanation was that the 1995 Romanian estimate was a result of the expansion of treatment facilities (from 12 in 1991 to 30 in 1997) and with a reportedly sudden increase in acceptance of new patients [122].

If the 1995 acceptance rate was applied to the population aged 15+ years the expected number of new patients on RRT would have been 2,196 of ESRF patients newly accepted on RRT for the year. Proportionately this would have been 69% of the 1997 stock (2,196/3,198*100). According to the data from the National Registry Report "acceptance varies very little in consecutive years; exception makes when an expansion of services has been significant"[223].

Given the various national acceptance and stock rates, in 1997, Romania could have expected between 11,000 and 37,000 individuals who were affected by CKD, in various stages of the condition or CKD states 1 to 5. A NHIF information report for 2006 gave a figure for CKD of 10,382 patients of whom 6,600 were on RRT [215]. However this could not be cross-checked against any other source, such as the MoH information for the same period, for size or CKD staging [150]. This represents almost 70% of patients with CKD stages 1 to 5.

Current epidemiological information systems monitoring (2008) does not allow valid assessment and ascertainment of numbers. Ten years on from when first data were collected through this research, very little progress has been made in relation with the quality of data collected or the information governance. For example, if the unmet need target was set at 10,000 individuals for 2008, given the reported figures of 6,600 for 2006 and 7,400 for 2007 and an expected CKD stock could be up to 37,000 individuals, then by 2008 around 67% may still represent unmet need. The upper limit of 37,000 is high and this is due to a very large confidence interval or explained by a small sample which gave a large confidence interval to the estimate obtained from the 1997 health survey [150;160;215; 227.]

4.4.6 Capture-recapture method to calculate the stock estimate

The two sources of information used were EDTA Registry (Section 4.1) and the Centre Questionnaire (Section 4.2). EDTA provided a list of centres which provided the data and this was independently cross-checked with the answer in the Centre Questionnaire to the question: "is the centre member of the EDTA-ERA?"

Table 4.2: CRM results: calculations for MLE and NUE

		Centre Questionnaire		
EDTA	*Yes*	*Yes*	*No*	
		616	989	1605
	No	534		
		1150		

(Maximum Likelihood Estimate) MLE = 2,996

(Nearly Unbiased Estimate) NUE = 2,995

95% CI for NUE of 2,995 patients was estimated from 2,869 to 3,121 patients in stock (at national level)

This range compares with a value of 3,170 stock of adult patients for 1998; 3,189 included paediatric patients [160]:-

The EDTA captured 54% of the 1997 stock (70% response rate) while the Centre Questionnaire only captured 38% (53% response rate). Both sources together identified 71% of the 1997 stock of patients (2,995 with a 95% CI from 2,869 to 3,121). A reported figure of 3,170 from the National Registry was just outside the upper 95% CI limit of 3,121 [227]; the calculated CRM estimate of 2,995 was used as starting point for the treatment model (Chapter 8).

After the CRM was applied, the national stock rate was estimated at 161.2 to 175.3 pmp in the population aged 15+ years. The reported national RRT stock rate for 1998 was 139 pmp; for 2003 this was 250 pmp, these values could not be checked for validity [122; 160;227]. The 1996 figure was also given in another source as 57 pmp which implies a nearly fivefold increase of stock in 10 years [122; 177]. The National Registry itself had less than 100% response in data collection in 2004. The reported figures therefore appear unreliable. The values obtained by this study are very different from any published figures.

In another example, in one of the 13 centres which responded to the CQ the highest value in this research was 222 pmp in 1997, in a centre from Transilvania. The lowest was 31 pmp. These variations may show inequalities in provision.

In 1998 there were 175 patient transplants throughout the country. No information was available on these individuals as the two transplantation units did not responded to the Centre Questionnaire and no details were given through the EDTA-ERA report.

Kidney transplantation is a legally regulated activity and mainly performed with kidneys from living related donors (82%). The law stipulates that transplantation can use cadaver kidneys, but Romania is faced with limited availability of organs, as in other western countries.

Because there was little information on transplant patients the final scenarios were based on transplantation data from the literature and the EDTA questionnaire (i.e. mortality, new transplants). The only available information on the existing transplant patients from the three units surveyed was that they all received living related transplants (LTx).

4.4.7 Resources

To summarise data from the Centre Questionnaire:

- there were 43 full time equivalent nephrology physicians, or 1 per 259,336 population aged 15-74 years. By 2003 an increase of 450% of nephrologists was reported compared with information from 1993 [177];
- there were 468 full-time equivalent nurses or one nurse per 36,848 adult population;
- there were 69 health care assistants and 58 other staff including: technical support and psychologists in the 16 centres. The ratio of physician to support staff was 1 to 3;
- haemodialysis equipment was, on average, 4 years old;
- the number of stations had doubled since 1995 in the Centre Questionnaire 16 centres: from 83 to 169 functional stations in 1997; furthermore there were 780 recorded in 2003, in line with the increase in stock of patients. The 2003 figure represents a 700% increase from 1991 (114 stations) to 2003 [122; 160];
- 25% of the functional stations were new (either purchased or obtained through charitable donations) in 1995; as many as 66% of the total were old or outdated and would have been replaced by 2003. For 1997 equipment figures the National Registry reported that "38% was new equipment, which was purchased and was not obtained through charitable donations". Information on the age of equipment was difficult to ascertain. The 2003 figures may include a 100% replacement of stations over 1997 numbers, but this could not be checked [122];
- of the 16 units covered by the Centre Questionnaire only 2 centres had 5- year and 8- year old equipment in use; 17% of the stations were non-functional. For the same year the Registry reported 31% non-functional stations, but there may have been different centres from the 16 centres which reported to the Registry. The equipment information was not available from the

Registry or the 16 centres. It was however apparent from unpublished documents that as many as 13 multi-national companies were sharing the renal Romanian market at the time;

- 14 on-line haemo-dia-filtration (HDF) stations (n=14) were purchased in 1997; this HD modality was recorded as available in 10 centres in 2003. However, the number of stations or patients attending such sessions was not given;
- artificial kidneys: 69% used cellulose membranes, 19% used both cellulose and non-cellulose and a small proportion (12%) used only non-cellulose membranes. The figures for 2003 data show an increase to 63% in the use of the latter type, which is described as more "bio-compatible", in a review by MacLeod from 1998 [125] and thus shows an uptake of the latest technology; this should assist in an indirect evaluation of quality of care and translated into 'better' outcomes (survival) on HD;
- HD dialysate buffer: 14 centres (88%) reported the use of acetate, one centre reported using both types (acetate and bicarbonate) and one using only bicarbonate. The literature shows the benefits of the use of bicarbonate over the acetate, by reporting that both cost the same, but the bicarbonate is better tolerated, thus improving treatment outcomes (survival). By 2003 nearly all HD centres (95%) reported the use of bicarbonate buffer; and for CAPD, only eight centres reported this form of RRT and six of them reported it after 1997; a Y connection was used with catheters connected to double bags identified as the standard delivery of this mode of therapy.

4.4.8 Provision of RRT in the three sampled units: stock and acceptance

The Centre Questionnaire results from the sampled units are shown in Table 4.4.

- Centre 1: Sf. Ioan, Bucharest. A teaching unit with a catchment area of just over 1 million population. The stock of patients was n= 322 during the 3-year period 1995-1997; of the 322 a sub-sample of 136 patients (42%) were newly accepted during this period.
- Centre 2: Iasi, A teaching unit with catchment area of 3.6 million population. The centre stock was 400 patients during 1995-1997; of the 400 a total of 158 (40%) were newly accepted in this period.

- Centre 3: "Sarah" Brasov, A district unit with catchment area of about 0.5 million population. The centre stock was n= 229 patients during 1995-1997 of which 83 (36%) were newly accepted in this period.

In each centre the majority of patients were treated with haemodialysis, the proportions varying from 78% to 95% (Table 4.4). CAPD had just been introduced in 1995. Although centre 2 was one of the country's pioneering centres for peritoneal dialysis, only three patients were treated there that year on CAPD, although reported numbers varied, 21 patients compared with 34 patients, according to the Centre's Register and as reported by the manager at interviews. The reported CAPD patients could not be validated against the number of patients for whom notes were available from the archive. Thirteen could not be found. The proportions of 14% to 19% were those of patients treated with CAPD in Centres 1 and 2 in 1997, and they were newly accepted on this form of treatment during that year.

Transplant patients, in proportions of 1%, 3% and 3% were recorded under this modality under each of the Centers' registers. Transplantation was actually performed in other reference centres, but once the surgical and peri-operative care have been completed follow-up care is carried out in the centre of their catchment area.

Ten patients had a transplant in 1997: one in Centre 1 (here shown as a proportion); 6 patients from Centre 2 (proportion of 3%) and 3 patients in Centre 3 (proportion of 3%) as shown in Table 4.3.

Table 4.3: Operational RRT activity from the three sampled centres (1997)

		Centre 1 Bucharest	*Centre 2 Iasi*	*Centre 3 Brasov*
Year in which centre was set up		1994	1990	1994
Catchment population (15+ years)		1,069,824	3,811,673	505,575
Acceptance*	1995 (% of stock)	62 (70)	66 (47)	30 (64)
	1996 (% of stock)	61 (55)	65 (44)	32 (53)
	1997 (% of stock)	48 (27)	52 (28)	34 (30)
rate pmp	1997	44.9	13.6	67.3
Stock**	1995	89	141	47
	1996	111	149	60
	1997	175	186	112
Rate RRT pmp	1997	164	49	222
Rate HD pmp	1997	138	38	210
Doctors (f/t)		8.5	7	3
Patients/doctor		21	27.5	37
Nurses (f/t)		60	36	25
Patients/nurse		3	5	4
RRT proportion on (1997):				
HD%		85	78	95
CAPD%		14	19	2
T_x%		1	3	3

The stock and stock rate by age group from the three sampled centres in 1997 are shown in Table 4.4:

Table 4.4 Stock on HD in the three sampled centres, 1997, by age group (15+ years)

Centre 1 (20 stations)	*<15*	*15-24*	*25-29*	*30-39*	*40-49*	*50-59*	*60-69*	*70+*	*All*
Stock no.	n/a	5	9	25	41	38	30	-	148
(%)		3	6	17	28	26	20		100
Stock (rate pmp)	n/a	25	76	161	211	273	203	-	138

Centre 2 (32 stations)	*<15*	*15-24*	*25-29*	*30-39*	*40-49*	*50-59*	*60-69*	*70+*	*All*
Stock no.	n/a	6	14	47	45	31	3	-	146
(%)		4	10	32	31	21	2		100
Stock (rate pmp)	n/a	7	33	84	71	66	6	-	38

Centre 3 (14 stations)	*<15*	*15-24*	*25-29*	*30-39*	*40-49*	*50-59*	*60-69*	*70+*	*All*
Stock no.	n/a	6	8	16	23	31	22	-	106
(%)		6	8	15	22	29	21		100
Stock (rate pmp)	n/a	54	145	188	226	517	410		210

The variation in stock rates between the three centres is partly attributable to the different sizes of their catchment areas. Stock rates go up with age as expected in all three centres, but as table 4.4 shows, there is substantial variation in the age distributions of their patients. This is partially explained by the demographic profiles of the regions they belong to but this needs further investigation.

4.5 Strengths and limitations of this element of the study

Amongst strengths are:

- The reported service use was available for the requested period for this research and was reported as cross-sectional information allowing for the description of a baseline year
- Some demographic detail was also available, especially from the 3 sampled units
- Staffing levels were reported
- Financial resources were available
- Due to the availability of data from two sources, further analytical methods allowed the estimation of a baseline stock level (rate per million population)

Limitations were also identified:

- The centre response rate was poor
- No precursor condition record for any of the patients, newly accepted or in stock, was available either at individual level (sampled units) or in aggregate format, at centre level
- Transplantation information was little to absent thus hampering the inclusion of local transplantation data in the treatment model
- Validation of information was not possible and neither were checks for precision or accuracy of reported estimates

4.6 Summary

Service use for CKD under RRT has established a baseline level for acceptance and stock for the year of 1997 after the use of quantitative and qualitative methods. Although the reliability of the estimates is low, the acceptance and stock rates can be used as parameters for the treatment model in scenarios applicable to local context.

5 Clinical outcomes

5.1 Objectives

The general objective in this chapter is to assist with the estimation of parameters for the treatment model.

It has the following more specific objectives:

- to measure observed outcomes (survival) for individual patients in three sampled units in Romania;
- to place the results in an international context and discuss them in relation to the treatment model.

5.2 Methodology and Methods

To assess clinical outcomes based on a sample of units.

5.2.1 Data on outcomes

Data were sought on three cohorts of new patients, entering renal replacement therapy in 1995, 1996 and 1997.

Table 5.1 summarises the data collected.

Table 5.1: Data collection points

Cohort	*Baseline data*	*1 year follow-up*	*2 year follow-up*	*3 year follow-up*
1995	1995	end 95-96	end 96-97	end 97-98
1996	1996	end 96-97	end 97-98	
1997	1997	end 97-98		

Appendix 5 contains the form used for data collection. It consists of baseline data and additional data sheets data for each year of follow-up. The baselines were from 1 January 1995, 1996 and 1997. The data collection period ended on 31 December 1998.

5.2.2 Inclusion criteria

All patients who were enrolled on a dialysis programme, or who had had a kidney transplant, were initially included, irrespective of the duration of treatment (see definition at the beginning of this Chapter and Chapter 2). Chronic renal replacement therapy patients became 'cases' after 90 days or more of RRT [60].

5.2.3 The units sampled

The initial design involved sampling six units. However it was discovered that one satellite unit was no longer treating chronic RRT patients. In two other centres there were problems in obtaining access to their patient database and register. Eventually only three centres were recruited: two teaching centres and a district unit.

The three centres were sampled according to their level of occupancy (patients/station) in 1997 with cluster analysis (SPSS 9.0). These centres are representative of three of the seven historical regions (Muntenia, Moldova and Transylvania) as described in the national health survey, in terms of both size of population and geographical location [163].

Consent was sought from the Ministry of Health from the National Commission for renal replacement therapy, which co-ordinates the RRT National Programme. Members of the Commission are clinicians but some of them combine clinical and managerial roles.

Consent was also sought at the Dialysis Centre/Unit level for access to individual patient records from the centre's manager or the chief medical officer of the centre/nephrology department. Consent letters were sent out to the three centre managers (Appendix 5) for patient data collection in 3 cohorts: 1995, 1996 and 1997 (Patient Form in Appendix 6).

The three units were as follows:

5.2.3.1 Sf. Ioan Teaching Hospital, Bucharest

This centre is located in the capital city of Romania, Bucharest, in district 4 (Bucharest has 6 districts). It is a teaching unit, attached to a general teaching hospital. Established in 1994, it is the second biggest and oldest centre in Bucharest. The catchment area for this RRT centre and the other renal services it provides comprises approximately 1,012,129 population (1998).

The letter of consent was sent to the dialysis centre manager to obtain access to the centre's database, registers and to the nephrology department archive. A two-person team ensured the data collection from this centre. Data were validated while researchers were on the premises.

5.2.3.2 C I Parhon Teaching Hospital, Iasi

This centre is in the north-east of Romania, and is the capital of Iasi county. It is an academic centre within a teaching hospital, providing health services for the city, county and the north-eastern region of Romania, Moldova, which has borders with Republic of Moldova and Ukraine. Established in 1990, it is one of the oldest centres in the country. The catchment area for this centre and the other renal services it provides comprises approximately 3,635,150 population in eight counties (1998). Since 2006 each of the eight counties has established its own centre.

The letter of consent was taken to the dialysis centre manager to obtain access to the centre database, registers and nephrology department archive. A second two-person team ensured the data collection from this centre and overlapped with data collection in the other two centres. Data were validated while researchers were present on the premise.

5.2.3.3 Sarah District Hospital, Brasov

The third centre is in Brasov, the capital city of Brasov county. This is one of the Transylvanian counties in the central part of Romania. The centre is attached to the district hospital of Brasov. In 1997 it provided health services for the city and surrounding county and partially for the region, i.e. counties which border with Brasov: Covasna and Prahova. This was the case in 1997. In 1998 the catchment population for this RRT centre and other services it provided was 486,183.

However, by 2006, it was reported that each of these three counties had set up its own dialysis centre. Set up in 1994, it belongs to a 'second generation' of RRT centres.

The letter of consent was sent to the dialysis centre manager to obtain access to the centre's database, registers and the district hospital's nephrology archive. A third two-person team ensured the data collection from this centre. Data were validated by the lead researcher electronically after the team completed data extraction.

5.2.4 Data collection timetable and analysis

Each Centre's Register provided a list of all patients who entered renal replacement therapy, i.e. haemodialysis or peritoneal dialysis between 01 January 1995 and 31 December 1997.

Baseline socio-demographic and medical data were taken from the Centre's Register.

Follow-up data were collected on subsequent co-morbidity, biological markers, complications, hospitalisation and other key events (transfer, loss to follow-up or death). The Centre's sources for follow-up data were: the Biological Tests Register, the RRT Register and individual clinical notes from the Centre's Archive. Data collection teams were trained by the lead researcher (during an induction day) to collect items according to a standard protocol across all three centres.

Total numbers of new and old patients were validated against the reported figures obtained from the CQ for these two centres. Eleven patients were the mismatch between the clinical records and the sum of patients from the 3 CQs (Figure 5.1).

5.2.5 Methods of survival analysis

The descriptive analysis of the sample from the three centres is shown in Appendix 7.

Patients who had been on treatment for less than 90 days were excluded. Survivor probabilities for 1, 2 and 3 years were computed by type of therapy for 1) aggregated cohorts (hospital HD, CAPD, transplantation), 2) by centre, irrespective of treatment modality and 3) by aggregated cohort and year of starting the RRT: e.g. 1-year survival for the 1995 cohort, 1996 cohort, etc. Patient survival probabilities, standard errors and 95% CI were estimated using both life tables and the product limit method (Kaplan and Meier). The Software used was SPSS 9.0. Five-year survival probabilities and survival by age-groups were taken from the literature [122; 180; 230].

Cox regression was used to identify prognostic factors associated with survival: first, variables were dropped if they had high values of correlation coefficients [231]. Same Software was used for this analysis.

Then logistic regression was run with a limited number of variables detected as clinically important: e.g. presence of diabetes and malignancies. These were systematically checked for statistical significance. The logistic regression was run with these variables as well as demographic ones using binary coding for presence or absence of: age equal or above 60 years,

gender, cancer, diabetes, hypertension, with cut-off points for time on treatment at 12 months and 24 months. Data from one centre met the 36-month time criterion; however, the number of patients became too small and data on co-morbidity (cancer) were absent, making the 3-year probability unreliable.

Model 1 included age ≥60 years, presence of: diabetes, and cancer as co-morbidity at baseline;

Model 2 included age ≥60 years, presence of: diabetes, cancer as co-morbidity at baseline and presence of complications during follow-up at 12-, 24- or 36- months.

A relatively low threshold of 60 years was chosen because of the relatively lower life expectancy at birth in the Romanian population. Survivor probabilities were subsequently used for guidance in the treatment model and hypotheses were made in the final chapter (Chapter 8) given the treatment capacity of the country.

5.2.6 Numbers of subjects

Clinical outcomes data were obtained from 3 of the sampled units.

For the three centres the total sample of newly accepted patients for 1995, 1996 and 1997 was N= 450 (Fig 7.1). Of these, 377 (84%) were eligible for descriptive analysis, as they had spent more than 90 days on RRT as per eligibility and so met the inclusion criteria; of these, only 236 (63%) had records usable for outcome measurement.

For patients with less than 90 days on treatment: 30 patients died; that is 7% mortality in the first three months. Twenty-seven (27) patients were lost to follow-up after initiation of treatment (6% of the original cohort of 450), of whom 12 patients had an initial assessment record and treatment plan but no other notes, and the remaining 15 had an assessment record and notes which showed they moved to another catchment area. Five (5) patients recovered their kidney function (1%) giving a total of 62 patients who were ineligible for data analysis and who were excluded.

F*or patients in treatment for longer than 90 days*: 11 patients were excluded due to poor records (e.g. no date of birth, no date of entry on treatment, recorded death, but with no month and/or year of death, etc.). Of these 11, 8 patients were from Centre 3. Centre 3 has the smallest

sample and therefore the survivor probability results for this centre as well as the LYG (life years gained) may be affected and they need cautious interpretation.

Figure 5.1 shows the sample and exclusions.

Baseline data were analysed for the aggregate cohort (N=377) as well as for each centre (n_1 =136, n_2 =158, n_3 =83). Table 5.3 shows the eligible number of patients in each centre, by cohort and those considered for the aggregate analysis of the survival at 1- year, 2- year and 3- years.

Fig 5.1 shows the total number of patients in the Centres' Registers. Data from newly accepted patients in 1997 (n=120) were sought on complications and hospitalization. However, these data were highly unreliable and the information was not used.

Figure 5.1 Sample size by centre

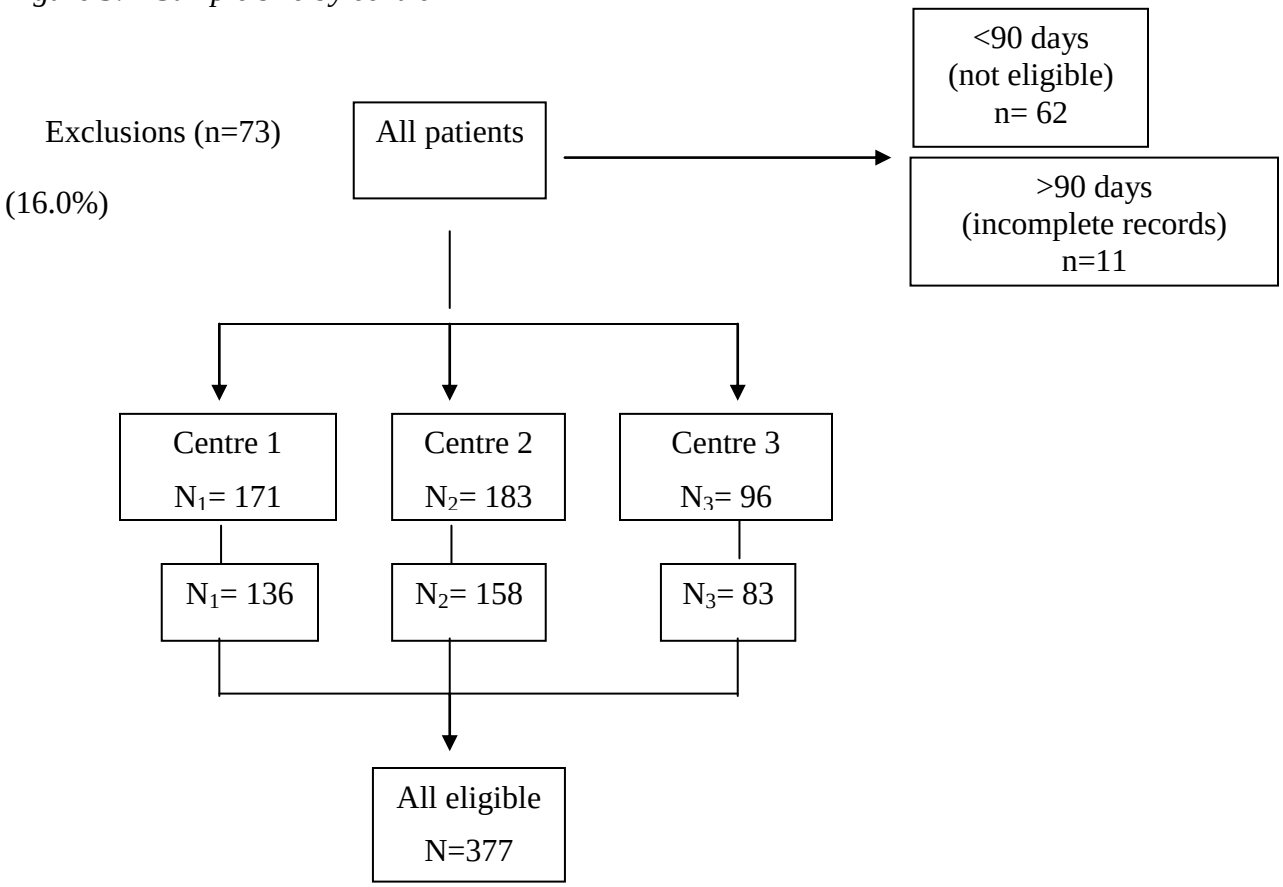


Table 5.2: Sample size of newly accepted patients, centre and type of RRT

Cohort	*1995**		*1996*		*1997*		*1995-1997*
	HD	*CAPD*	*HD*	*CAPD*	*HD*	*CAPD*	*Total (%)*
Bucharest	42	-	43	6	34	11	136 (36.1)
Iasi	53	3	48	12	32	10	158 (41.9)
Brasov	23	-	27	-	33	-	83 (22.0)
Total	118	3	118	18	99	21	377
*Total for adjusted survival***	53	3	48	12	99	21	236

** Tx patients are not included anywhere (insufficient data)*

*** Cox regression was carried out on aggregated cohorts of new patients: centres 1 and 3 for 1997; centre 2 for all new patients: 1995, 1996 and 1997 (in Bold).*

Table 5.1 shows that the uptake of new patients was fairly constant over the three years. Centre 1 had 42 new patients in 1995, 49 in 1996 and 45 in 1997. There is a slight decrease in those entering HD in 1997 when the uptake on CAPD increased over 1996 in Centre 1 and Centre 2 but not in Centre 3 where between 1995 and 1997 the increase was 43% with acceptance only on HD.

The underlying ESRF diagnosis was similar in all three centres, also similar to reports in the published literature [103; 122].

There were no data available for any socio-demographic analysis e.g. on education, occupation (at baseline and follow-up), marital status or residency. There were data on the means of transportation to and from the RRT centre. All patients used the centres' ambulances (none used urban or inter-urban public transport or private cars). A descriptive analysis of the sample is shown in Appendix 7.

5.3 Treatment outcomes: survival

5.3.1 Unadjusted survival

Romanian patients on RRT tend to be younger when accepted on treatment than their peers in other western societies: age was: mean 42 years; median 43 years and modal value 45 years.

There were 30 to 50% more male patients than female patients overall (228 males/ 149 females), a pattern seen in all three centres (Appendix 7).

The unadjusted survival probabilities at 1- , 2- , and 3- years were: 84% (79 to 87%), 73% (69 to 78%) and 68% (62 to 74%); 1- year survival is significantly higher; 2- and 3- year probabilities do not differ statistically. They can be compared with 86% (1-year), 78% (2- year) and 71% (3-year) for the 1997 English cohort [232]. By treatment modality these were HD: 83%, 73% and 67% with differences noted not to be statistically significant; CAPD: 1- and 2- year only: 90% and 81%. Survival by RRT modality did not differ at 1- and 2 years; CAPD had only n=36 new patients; confidence intervals (95% CI) were very large.

No differences were observed in the survivor probability at 1 year by cohort ("vintage"): 82%, 87% and 82% for 1995, 1996 and 1997 newly accepted patients; this again compares with 86% in the 1997 English patients. At 2- year the 1995 and 1996 patients showed a small, but not significant difference: 70% and 77% respectively. The observed 3- year probability for the 1995 cohort was 65%. The 1997 English cohort had a 71% probability [232].

Results for survival fell in the expected range as reported in the literature [122]. Any differences could be also explained by factors such as: age at entry on treatment, cause of CKD5 (primary renal disease predominant in Romanian patients), presence and type of co-morbidity, number of complications developed during the next 12 months of RRT, etc., or age and co-morbidity combined. The extreme age groups in Khan index refer to a $<$ or $\geq$ 70 years old. However, with no patient in this study being this old, this index proved to be of no use for the Romanian data [5].

Estimation of survival by modality was very difficult with the information held on clinical file. At the introduction of CAPD in 1995-1997, most patients did not die on this modality. One explanation was that they may have been allowed to switch therapies: e.g. if a CAPD patient developed an irreversible complication on this mode or "showed no improvement in clinical status and general well-being" i.e. including a lowered serum creatinine level, or changes for the better in other biological markers (e.g. parathyroid activity levels etc.), the quick solution was to switch them on to HD. These were most frequent explanations in the two centres which offered CAPD as an RRT modality and from the answers recorded at local interviews. This was also given as possible reason as to why CAPD notes were not found on the CAPD Register.

However in this analysis CAPD patients were considered to have stayed on CAPD for one year even if they switched modality before the year elapsed. This is similar to analyses in other studies [60]. To clarify, if the switch to another form of RRT took place after 60 days from entry on RRT, on top of the 90 days already on RRT for the purpose of data analysis, the patient would be kept for the year on the original form of treatment and would be changed only after 31 December (i.e. December 1998 in this study).

As a new therapy, CAPD being only introduced since 1995 in a few centres, one cannot conclude whether this modality was an alternative to haemodialysis or whether it was good practice in offering a new alternative of treatment in Romania. This marked the introduction of the 'safety valve' of RRT in Romania which allowed the extension of life for ESRF patients who otherwise would have died in a much shorter period of time. It is also unlikely that the analysis of data on the total of 36 patients brings significant information at this point, but it was thought to be worth exploring this sub-sample as the treatment model includes this form of therapy.

5.3.2 Cox regression

This statistical method allows adjustment for variables which may have an influence on the survivor probabilities or time. The unadjusted Cox regression analysis used data from all 377 patients. Age (equal or above 60 years), diabetes, cancer and the presence of complications in the first year of treatment were considered in the Cox regression with survival time considered at one, two and three years. The one-year survival probability was significantly influenced by the presence of cancer or a combination of age $\geq$ 60 years and co-morbidity: diabetes and cancer. A Poisson distribution model was used. Two models were used: one with gender included; a second with this variable excluded. Table 5.2 presents the results from the second model (gender was not statistically significant).

After running the 12, 24- and 36- month period for two models non significant variables were dropped until scenarios showed age and co-morbidity associated with the 12-, 24- and 36 month survival.

The 2- year probability was significantly influenced by: a combination of age $\geq$ 60 years, diabetes, cancer and the presence of complications (binary variable) in the first year of treatment;

The 3- year probability was significantly influenced by the presence of diabetes.

A summary of the statistically significant unadjusted coefficients are shown in table 5.3:

Table 5.3: Unadjusted coefficients from Model 2, Cox regression (n=377)

	B coefficient (unadjusted)	*SE (standard error)*	*P value*	*Notes*
Age	1.23	0.39	0.001	1-year survival
Diabetes	1.14	0.55	0.038	
Cancer	3.03	0.59	0.000	
Age	1.96	0.68	0.004	2-year survival
Diabetes	1.32	0.58	0.023	
Cancer	2.66	1.09	0.015	
Complications	1.65	0.59	0.005	
Diabetes	2.15	0.92	0.020	3-year survival

Survival appears to be significantly influenced by a combination of age and specific co-morbidity here defined as the presence of diabetes and cancer; this is despite the fact that Romanian patients tend to be younger than western patients. It also appears to confirm results from the literature such as the North Thames Dialysis Study (NTDS) in which gender was not shown significantly related to survivor probabilities, despite the greater proportion of men on RRT [232]. Also, the NTDS had an older age profile.

The observed 3-year survivor probability is smaller than those observed in Western societies (e.g. England has 60% and 50% at 5 and 8 years; results are taken from a study initiated in 1997, same year as this study took its survival data from) [230] .

Precursor condition morbidity, such as PRD at baseline and gender did not show any influence on any of the three survivor probabilities (excluded from Table 5.3); moreover, when the presence of "complications" was dropped from the regression model, a change occurred in the 2- year survivor probability: cancer, now had an unadjusted B coefficient of 2.40 (p= 0.000; SE= 0.53) and remained statistically significant, whereas diabetes, with an unadjusted B coefficient of 0.80 (p=0.09; SE= 0.47) became a statistically non-significant variable. Table 5.3 also shows that diabetes has an increased hazard (risk of death) from 1.14 in the first year to 2.15 in the third.

5.4 Strengths and limitations

Strengths:

- The results in this Chapter have further added to reported information through first hand analyses of 1- to 3- year survivor probabilities from 3 local sampled units
- The annual survivor probability and annual mortality was used as parameter in the treatment model (dialysis only)
- Because of the availability of individual data, it was possible to exclude deaths which occurred in the first 90 days of RRT, increasing the validity of comparative survivor estimates

The limitations are numerous:

- Samples were too small to adjust and present for age, gender or treatment modality
- Diabetes was a 'rare' condition (< 5 cases/ the 377 sample of patients); very wide confidence intervals showed no statistical significance for hazard ratios (B coefficients) and makes the interpretation of the increase from 1.14 to 2.15 inconclusive
- Co-morbidity was insufficiently registered and thus not possible to be better described an analysed
- Transplantation patient data were not available, therefore survival from this modality was not measured from local data; Tx information on this parameter had to be taken from the literature
- Despite the individual data from 3 centres, the information may not be representative for all adult centres (30 centres) across the country
- A 5-year observed survivor probability was not calculated; only 3-year data were available

5.5 Summary

- Over three years a total of 450 patients entered RRT in the three centres. A total of 377 were eligible for descriptive analysis; 236 patients had usable data for clinical outcomes (survival analyses).

- 90% of patients were on HD. Almost all the rest were on CAPD. The number of patients having transplants was very small.
- The demographic data show that the Romanian RRT patient is most likely to be a middle-aged male patient (modal age in sample 45 years and 30-50% more male patients);
- Survival for HD was: 83% at 1 year, 73% at 2 years and 67% at 3 years. For CAPD it was 91% at 1 year and 81% at 2 years. These figures for CAPD need to be interpreted cautiously due to the small number of patients (n=36), but they are consistent with the literature from elsewhere.
- In the Cox regression the main factors related to survival were age and co-morbidity (diabetes and cancer); gender was not a significant factor in this small dataset. The role of obesity could not be assessed because physical measurements of weight and height were not available.
- The literature suggests that age in isolation does not influence survival. Cardiac and social causes are most quoted as possible predictors for mortality, but these could not be assessed from the data available.
- Late referral, as a predictor of early death on treatment, may also vary very widely across countries, depending on the definition of 'late' which is or is not preceded by nephrological care. This remains a possible explanation for the variation in early case fatality on RRT which in turn influences survival, as outcome, on treatment. However, time to referral, as a covariate, was also not included in the original research protocol.
- There was no evidence that co-morbidity (PRD) at baseline (excluding DM and cancer) influenced survivor probabilities in the Cox regression. When the presence of complications in the first year of treatment was excluded as a variable in a second Cox regression model, all parameters remained unchanged with the exception of diabetes which became a statistically a non-significant factor for survival of up to two years on RRT.
- The half-life (median survivor probability or time at which 50% of the initial cohort is still on treatment) of the Romanian RRT cohorts was between three and four years [29]. Regarding co-morbidity and survival, the diabetes literature suggests that type 2 diabetes patients have a worse prognostic on treatment outcomes (survival) than type 1 diabetes ones (ref) and this is in

contradiction with the “inverse epidemiology” regarding obesity on RRT, knowing that obesity is strongly associated with type 2 diabetes.

6 Treatment cost estimates in sampled units

6.1 Objectives

The general objective is to look at the economics of treatment of CKD5 in Romania: how much does it costs and, how does it compare with other countries when accounting for effectiveness. This Chapter has the following specific objectives:

- to measure the cost of illness (CKD5) in three sampled units;
- to estimate the average cost per patient by alternative therapy: HD and CAPD; and maintenance cost for a Tx patient;
- to estimate the cost-effectiveness ratio for i) no treatment versus any dialysis alternative and ii) HD versus CAPD.

6.2 Methodology and Methods

6.2. 1 Data on inputs and costs

Data on costs were gathered during interviews with the local key persons, financial managers and clinical nephrologists, using specially designed forms (Appendix 8 and 9).

Data on human resources were taken from each Centre's Personnel Department. Data on biological tests and their costs were obtained from each Centre's Head of Pathology Department attached to the district or teaching hospital.

The costing framework and the purpose cost form were adapted from the literature and translated into Romanian [1; 186].

Accounting data were gathered during interviews with key financial personnel for volume of activities, overhead costs, etc., with clinical specialists or head nurses for consumables by type of RRT and from heads of Personnel Departments on numbers of employees, salaries, etc. Staff costs were estimated from activity sheets. Overhead (semi-fixed) costs were also collected. The interview form is shown in Appendix 10.

Each item identified as a main cost component was further sub-listed for each type of treatment: HD, CAPD, LRTx. Costs on transplantation were taken from the literature as local costs were

difficult to document, difficult to validate where they were available and also considered unreliable.

The steps in estimating total programme operating costs were:

1. Estimate costs of outputs:
   - Haemodialysis session and haemodialysis/ year of treatment
   - Continuous Ambulatory Peritoneal Dialysis training session and subsequent yearly treatment
   - Transplants costs (taken from literature and the NHIF, 2007 [233].

2. Calculate annual average cost of HD treatment from the number of dialysis sessions per patient-year in the three centres.

3. Calculate annual average cost of CAPD based on the initiation session and the variable component of this cost (i.e. treatment at home, ambulatory).

4. Estimate Transplant costs based on the maintenance medication documented in all centres as well as from the National Register.

6.2.3 Overhead costs

Shared costs (overheads) were considered, although in a short-run cost analysis they would not change much [1]. The direct allocation method was adapted from Churchill et al [186]:

- For centres 2 and 3: building maintenance (cleaning, disinfection, porters/receptionists, administration, heating, telephone lines, laundry, kitchen and cafeteria); administration of wards, pharmacy, supplies, X-ray department, laboratories, changing rooms, common areas and all rooms where renal replacement therapy linked activities are identifiable
- For centre 1: hospital overheads (all of those listed above, but related to the hospital building or inpatient wards, plus teaching and research)

This study excluded non-market items (e.g. volunteer and carer time, patient/family leisure time, etc.). It did not consider 'price' adjustments if, for example, a centre had a local monopoly and where "access charges" may have deviated from costs. This is because this economic study was not purely undertaken from the viewpoint of a third party payer (i.e. for whom charges may be more relevant than the costs).

This study considered included two types of patients' payments (or cost-shifting): travel costs (if patient covered the costs from her/his own pocket) and medication by prescription (the out-of - pocket component). However out-of-pocket prescription costs were excluded because no data were available.

An attempt was also made to measure opportunity costs, particularly for capital revenues (land and buildings) but this was abandoned as too unreliable. Guidance from Churchill and Torrance was applied.

6.2.4 Cost- effectiveness analysis

For Centres 1 and 2 the cost/life-year gained was computed by type of therapy. Centre 3 treats patients with HD only. A weighted average RRT cost per centre and therapy was computed. Transplantation could not be included in this analysis due to lack of sufficient information.

Life-years gained (LYG) were computed as the sum of months alive on a therapy in a year for all *new* patients treated in that centre, for the given year, 1997.

Costs for the first year of treatment (1997) were distinguished from the expected costs in the later years on treatment to allow discounting. The cost-effectiveness (C-E) baseline ratio was calculated for the first year of life gained on RRT, for the 1997 cohort.

The final cost/ LYG was given by the total cost of treatment for new patients (proportionate centre's total cost) divided by total LYG [1].

6.3 Budgeting, expenditure & costing at national level: National Registry report

According to the Ministry of Health, in 1995 the "Programme for development of Nephrology and Renal Replacement Therapy" spent the whole of its budget of US$ 17[1] million for the reported 1,325 patients in stock (Ministry of Health, 1996) [177]. According to the Romanian Society of Nephrology Annual Report the budget for the previous year, 1995, was US$ 15.8[1] million for 1,301 patients in stock (Tables in Appendix 8) [177]. Regardless of the source used, the sum accounted for approximately 1.7-1.9% of the health care budget and, on average, the annual cost per patient was estimated at US$ 12,145- 12,831. These are high costs per patient in Romania, and RRT is considered to be a therapy with an economic impact on the health care budget as a whole.

However, there were no reported figures on expenditures and on how much the Programme overspent. The Programme was reportedly overspent in 1997 but information came from the limited numbers of centres which responded to the Centre Questionnaire (Chapter 4).

In the financial section of the Centre Questionnaire most centres who answered to this question revealed a negative balance at the end of fiscal year with a median deficit of 21% (Chapter4). Inflation and other macroeconomic aspects may have had an impact on this tertiary service as any of the other budgetary sectors since 1997. Ten years later, inflation had stabilised at 6-7% (2007), yet at 2010 level budget was again under threat. Over a third of centres were privatised since 2008 and as a new practice the economics of these centres was not assessed [234]

According to interviews with National Key Persons, "the Programme's budget is set in accordance with the patient's average cost on each mode of RRT." This historical principle ruled the annual budget of the RRT National Programme; it was still the case in 2007.

The share of money from the health budget is highly competitive. Each health care area has to negotiate their own budgets and, it is often the Health Minister that decides "who" gets "how much" making RRT a top political decision; negotiations can often take as long as half year and this was the case in 1998. By 2003 RRT had become an established tertiary health care area, distinguished from Nephrology which had become a branch of internal medicine.

Table 6.1 summarises from secondary sources the annual costs of the RRT patients.

Table 6.1: *Total annual programme estimated cost of RRT, Romania, 1995 and 1997 (USD)*

Year	*HD*		*CAPD*		T_x		Total Programme Cost (US$) (weighted ∑ according to proportion of patients on each type of RRT)
	Cost/patient	*% patients*	*Cost/patient*	*% patients*	*Cost/patient*	*% patients*	
1995	12, 796.8	-	15, 686.4	-	7, 759.2	-	15, 824, 613.6[1]
1997	14, 946.4	82	16, 595.9	11	7, 588.8	7	35, 171, 448.8

In 1995 and 1997 around 82% of patients were on HD, the rest had either a transplant or were on CAPD. The figures for this estimated Total Programme Cost are rough. The Total Cost should be interpreted with caution. This is because the RRT Programme's budgets and expenditure for these

years were not obtainable from any of the Reports of the National Renal Registry or the Nephrology Commission in the Ministry of Health. The reported figure of US$ 17.1 million for 1995, which this study estimated at US$ 15.82 million was an exception. It seems that, although under major constraints, by 1997 the health care system could afford to more than double the proportion of budget allocated to this type of care.

According to the responses to the Centre Questionnaire, eleven centres reported a total budget of US$ 7.9 million, and a total expenditure of US$ 9.1 million, with a balance of US$ –1.2 million or a -22% deficit.

Financial resources: eleven centres of the 16 asked answered this question. With the exception of two centres which reported expenditure matching the budget, all respondents were "overspent" at the end of fiscal year. One local key interviewee explained that "…the programme is under-funded…"; and "due to the fact that trends in overspending "are customary" and centres know that their future budgets are drawn on a historical basis, with no adjustment for need whatsoever, overspending is not a problem" (local interviews).

On average, the reporting centres were overspent by 22.3% (median: 21.3%); there have been other financial and accountancy explanations, too, but information was limited and time was insufficient to explore this further. 2007 data showed that the RRT network matched 98.1% of the allocated budget in expenditure.

No further breakdown of financial information was available.

6.4 Cost of illness

6.4.1 Annual cost of haemodialysis

For 1995 and 1997 the National Registry reported the average cost of a dialysed patient as follows (Table 2 in Appendix 8):

> 'the cost of HD treatment in Romania is low [US$ 87for a HD session]...operating costs represent almost all of it [US$ 81] and consist mainly of consumables and drugs ' (1995); we add the fact that, if a treatment is provided three times a week, the reported monthly average cost is US$ 1,066.4/ patient and the annual sum would be US$ 12, 796.8; 'as of

1997, the reported annual cost of an HD patient (allowing for an average number of 3 sessions/week) is US$ 14, 946.4; the figures give a US$ 95.81 per HD session.'

These figures were included in the National Registry Report, 1995: US$ 95.81/ HD session. The report used this figure which was then multiplied by the reported average of 154-158 sessions/year to obtain an average cost per HD patient [27].

On this basis, to treat a haemodialysis patient would have cost US$ 14,754.74 to 15,137.98 per year based on cost per session x 156 sessions (3 times a week is the average). This reported cost was higher than expected given the estimated values obtained from the sampled units in this study (Section 6.4; Table 6.6).

6.4.2 Annual cost of CAPD

Table 3 in Appendix 8 shows the reported accounting costs for this modality of treatment:

'the monthly average cost of a patient on CAPD is US$ 1,307.2' [an annual total of USD 15,686.4.]

'…as of 1997, a CAPD patient would bring us to a total cost of $US 16,569.4 and USD 5,725.3 (or 35%) would cover only the initiation of treatment [28 days on average]'

It was also commented that CAPD was 'more costly' in Romania, 'as compared with the cost of this modality in other countries'.

6.4.3 Annual cost of a kidney transplant

Table 4 in Appendix 8 shows the reported accounting costs:

'it is the least costly method of RRT and on a monthly basis such patients cost USD 646.6, (an annual cost of USD 7,759.2' in 1995).

Note that the cost components did not include e.g. HLA tests, organ 'prelevation', surgery and immediate and long term postoperative care (e.g. testing the immune response).

In 1997, a kidney transplant patient would cost US$ 632.4 a month, of which 93% represents the cost of drugs, thus giving an annual total cost of US$ 7,588.8; it remains the 'cheapest' type of RRT'.

All costs in Appendices 8 and 9 were reported as accounting costs.

6.4.4 Results from sampled centres (volume of activities and total costs)

This Section presents the results from costs in the three sampled units which provided additional local details on the costing of their RRT. Cost data obtained from interviews with the finance managers were analysed and results are summarised in Table 6.2 (Tables are in Appendix 8).

From figures in Table 6.2:

- Overhead costs account for 6.7 to 7.6%. This is well below the reported national range of 22 to 28% in all three centres. However, when accountants recommended the inclusion of salaries in the overhead costs, the proportion increased to 20%. Including salaries as suggested could explain the observed difference between 7% and 20%. At interviews, accountants reported that all salaried personnel were employed on "permanent" basis and therefore these moneys are included in "fixed direct costs";
- Three main categories of staff were considered: doctors, nurses and health care assistants. However, for example, registered nurses who represented the largest proportion of staff working in RRT care could be employed in similar specialties if for example there were major fluctuations in RRT provision, such as centre closures. Also, it was not very clear, what was the basis for the calculation of the reported national figure of the overhead cost (22 to 28%)? From this study's perspective these costs were equally and directly allocated to RRT patients, regardless of the RRT modality in the first instance.

Variable costs account for the greatest proportion 80%. There was no national reported figure to validate against this kind of costs which represents the significant cost component and which could present variations. It was assumed that since reported fixed costs accounted for 22 to 28%, the variable component was implicitly set at 72 to 78% and this is sufficiently close to the 80% estimated value.

The average annual costs of treating a patient on RRT in these three centres are summarised in Table 6.3.

The average costs for a RRT patient with exclusion of salaries from the overhead (fixed) costs are presented in Table 6.2 (related to the Cost Form in Appendix 9).

Table 6.2 Total costs in the three sampled centres, FY 1997

Cost item	*Sf Ioan*	*Iasi*	*Brasov*	*Romania*
Building				
Year of built/ opening	1982	1996	1938	
Area (m^2)	660	788	430	N/A
US$/$m^2$	75^	20	35	
*Total building (at 1997 opportunity costs)**	49,500	15,760	15,050	
Overhead costs				
Water	15,192	14,797		
Electricity	23,856	19,343		
Gas	8,900	7,979		
Heating	47,960	11,318		
Lift	N/A	2,176		
Waste	2,265	2,454	72,534	
Inventory of assets*	24,420	21,518		
Cleaning	2,901	2,507		
Laundry	5,620	5,507		
Phone	1,939	2,902	1,088	
Ambulance	11,001	23,694	12,814	
TOTAL (%)	*144,053 (6.7)*	*114,195 (7.4)*	*86,436 (7.6)*	*(22 – 28)*
Salaries				
MD (f/t)	10,992 (4)	30,789 (7)	13,195 (3)	
Nurses	253,627	145,451	108,680	
Health care assistant	11,534	6,519	10,432	
Other	4,576	6,258	1,877	
TOTAL Salaries	280,730 (13.2)	189,018 (12.1)	134,184 (11.8)	
TOTAL Salaries including OC (%)	424,783 (19.9)	303,213 (19.5)	220,620 (19.4)	
Variable cost				
Consumables dialysis	1,061,533	1,078,377	710,397	
Drugs (co-morbidity)	641,647	159,776	196,091	
Pathology (routine)	16,453	13,941	8,117	
Food	4,292	786	1,992	
TOTAL (%)	1,723,925 (80.1)	1,252,880 (80.5)	916,597 (80.6)	
TOTAL COST /YEAR	2,148,707	1,556,093	1,137,217	

* building opportunity costs and "inventory of assets" comprising of assets such as ward furniture, etc ; these costs have become obsolete under 2008 economic circumstances and hence may have become a significant component of the 2008 RRT cost, well above the 6% discounting levels since 1997 (^e.g. one m^2 land in Bucharest stood at Euro 1,500 to 2,000 in 2008)

The adjustment in the overhead costs reflects costs included by type of treatment. CAPD patients are not provided with meals, except in the first month when they start treatment as inpatients. Transplanted patients are not provided with meals and do not use dialysis consumables, etc. Nurses as the largest proportion of the human resources employed by RRT units are mainly dialysis trained specialist nurses; they work in shifts at the centre, therefore HD patients would mostly benefit of their care.

An international comparison shows that Romania's annual observed/ measured cost per CKD5 HD patient differs from UK costs and other countries' costs and may only be comparable to Australia; these costs were measured for patients under RRT mainly for their first year under treatment;. It was difficult to distinguish the "new" transplant patient from the transplant patient "in stock" and the assumption was made that these results can be used for a "new" transplant [235].

Table 6.3 Annual average cost in sampled units, 1997 (US$)

Cost item	*Sf Ioan*	*Iasi*	*Brasov*
Total cost RRT programme (US$) of which:	2,148,707	1,556,093	1,137,217
Overhead costs (salaries incl.)	424,782	303,213	220,621
Variable costs –dialysis related	1,065,825	1,079,163	712,389
Variable costs – drugs and pathology	658,100	173,717	204,207
Total variable cost	1,723,925	1,252,980	916,597
No. of patients on RRT	175	186	112
No. of patients on HD (%)	148 (85)	146 (78)	106 (95)
No. of patients on CAPD (%)	25 (14)	34 (18)	3 (2.5)
No. of Tx patients (%)	1(1)	6 (3)	3 (2.5)
Average cost /RRT patient/year	12,278.3	8,366.1	10,153.7
Average cost/HD patient/year*	12,333.3	8,536.1	10,327.0
Average cost /CAPD patient/year**	12,008.7	8,551.2	10,664.2
Average cost /Tx patient/year***	10,828.8	3,179.5	3,540.2

*proportion of (overhead costs +consumables + food + drugs and pathology)/ HD patients; **proportion of (overhead costs + consumables + drugs and pathology)/ CAPD patients; ***proportion of (overhead costs + drugs and pathology)/ Tx patients

6.6 Cost effectiveness analysis from the sampled units

6.6.1 Cost of a life-year gained (LYG) on RRT by type of therapy in the three centres (CEA)

Table 6.4 shows the cost/ unadjusted LYG:

Table 6.4: Cost/ unadjusted LYG[§] for RRT patients in sampled units (1997)

Cost (USD) and LYG	*Bucharest*	*Iasi*	*Brasov*
Total cost dialysis (weighted HD + CAPD patients)	2,148,707 (HD=149; CAPD=25)	1,556,093 (HD=146; CAPD=34)	1,137,217 (HD=106)
Total cost dialysis (new HD patients)	419,862.3 (HD=34)	276,638.8 (HD=32)	353,700.23 (HD=33)
LYG on HD	29	27	31
Cost/ LYG HD	14,478.0	10,245.9	11,409.7
Total cost dialysis (new CAPD patients)	135,837.8	86,449.6	N/A
LYG on CAPD	10.4	9.7	N/A
Cost/ LYG CAPD	13,061.3	8,912.3	N/A
Total dialysis patients 1997 (new HD + new CAPD)	555,700.1 (HD=34; CAPD=11)	363 088.4 (HD=32; CAPD=10)	353 700.23 (HD=33)
LYG/ centre	39.4	36.7	31
Cost/ LYG RRT	14,104.1	9,893.4	11,409.7

§ total life year gained with no adjustment for age, sex, presence of co-morbidity, etc.

Three CER (cost-effectiveness ratios) were calculated and results described are:

i) cost of HD per life-year gained over no RRT:

Centre 2 and 3 appear to be more cost effective than Centre 1: US$ 10,245.9/ LYG (Iasi), US$ 11,409.7/ LYG (Brasov) compared with US$ 14,478.0 (Bucharest). If Centre 2 (Iasi) is taken as reference then cost/ LYG on HD in Centre 3 exceeds this reference by 11% and in Centre 1 by 41%. However, centre 2 has a younger population of patients in treatment and most likely less other co-morbidity. Costs are not adjusted (Table 6.2).

ii) cost of CAPD per life year gained over no RRT:

Centre 2 also appears to be cost-effective compared with Centre 1 for CAPD (Centre 3 does not provide CAPD). If Centre 2 is taken as reference then cost/ LYG on CAPD in Centre 1 exceeds by 47%. However, the number of new CAPD patients was small in both centres in 1997 (eleven in

Centre 1 and ten in Centre 2) and the difference, although apparently significant, could be explained by other unidentified factors. These ratios are also unadjusted.

iii) cost of HD/ 1LYG over the cost of CAPD/ 1 LYG (HD/CAPD ratios):

- Centre 1: CE ratio HD/CAPD = 14, 478.0/ 13,061.3 = 1.11;
- Centre 2 : CE ratio HD/CAPD = 10,245.9/ 8,912.3 = 1.15.

The above is interpreted as: one life year gained costs 11% more in Centre 1 and 15% more in Centre 2 to treat a patient with haemodialysis over a patient treated with CAPD. Both are teaching centres. The 4% difference is not statistically significant. These ratios are not adjusted in any way.

6.7 Strengths and limitations

The economic analysis shows limited strengths defined as:

- Availability of reported national and local costs by treatment modality
- Ability to calculate life-years gained from individual data from the baseline cohort of new patients who entered RRT in 1997;
- The size o financial resources were identified at 0.5% to 1% in the annual 1997 healthcare budget (figures in the literature give a proportion of 1-2%), thus allowing the benchmarking for financial resource allocation in Romania.

Again there were many limitations with the secondary information or the analysed data:

- The CEA could not include: observed costs of transplantation from either of the 3 centres which provided local costs for the other two treatment modalities; and could not include calculated LYG for Tx;
- setting assumptions such as the costs of transplantation surgeons was extremely unreliable and results would have been most likely invalid;
- limiting the Tx treatment to “maintenance” with immune suppressive drugs is insufficient, but no information was available for transplantation;
- the CEA is limited without ICER (incremental cost-effectiveness) information;

- the limited availability of utilities, which could not be validated, did not allow a calculation of QALY per RRT patient in Romania; or the cost/ QALY; the CUA would have given further insight in the economics of this clinical area;
- it was not possible to apply discounting to costs due to the economic uncertainties and high inflation which were marking the 1997/1998 period; and
- for the same reason, opportunity costs could not be estimated.

6.8 Summary

- RRT is an expensive high technology health care activity with significant life saving for renal patients.
- When benchmarking against the centre with the lowest cost/life year gained (Centre 2), the other two centres vary by 11% and 41% excess; this may have implications when recommending cost-effectiveness to be taken into account in resource allocation and related RRT policy.
- CAPD appears to be between 11% and 15% more expensive/life year gained than HD; however, this information is unreliable due to the very small numbers of cases on which it is based.
- Romanian costs appear to be similar to Australian costs (HD, first year), yet the two countries have very different purchasing power parities for the %GDP on health. Given that the costs were estimated from three centres only, more accurate cost measurements are needed. A more health economic approach based on ICERs (incremental cost-effectiveness ratios) would provide better support for budget planning.
- Planning, including budgeting is made on a historical basis; there have been "incentives" to become over-spend in both systems: 1) During the Semashko system "one patient's costs was another patient's benefit" (money was taken from other healthcare to cover for financial gaps; 2) During the NHIF system the RRT network has become reliant on the solidarity fund; 3) either system, with deficiencies in GDP% spent on healthcare, relies on unregistered "out-of-pocket" money; these aspects were beyond the scope of this study, but are further discussed in Chapter 9.

7 Policies, protocols, guidelines and existing provision

7.1 Objectives

The objectives of this chapter are:

- - to improve on the national and local quantitative information with qualitative information related to national RRT policy and its local applications; to cross-check information obtained at interviews with that available from secondary data sources such as official reports and papers from the grey literature.

7.2 Methodology and Methods

The methodology for this part of the study was qualitative. Semi-structured interviews of national and local "key persons" informants were used, the agenda being to identify current policies and protocols; and to assess local adherence to them.

7.2.1 Data sources

7.2.1.1 National key person interviews.

Five individuals at national level were interviewed:

- A lecturer in Nephrology (teaching unit), who worked part time for the National Registry of Dialysis and Transplantation *(I_1)*
- A consultant in Public Health, who worked part time for the National College of Physicians; since 2005 Professor in Public Health Medicine *(I_2)*
- A consultant nephrologist, president of the National Committee of RRT, MoH *(I_3)*
- A consultant nephrologist, Reader, Secretary of State, National Health Programmes, MoH *(I_4)*
- A consultant nephrologist, Professor and manager of the National Registry of Dialysis and Transplantation *(I_5)*

These interviews took place at the subjects' workplaces. The form used is in Appendix 10. The time taken ranged from 15 minutes *(I4)* to 4 hrs *(I2).* The interview dates were within three days of each other.

7.2.2 Local key persons interviews in sampled centres (Appendix 10)

The same three centres were used as for the outcomes data from the centre questionnaire (Section 5.2).

The local key interviewees were:

- The manager of the RRT Centre or the Clinical Director of the RRT Centre or Department (consultant nephrologist) (all three centres)
- The financial manager or (hospital) accountant (all three centres)
- The head nurse of the haemodialysis and of CAPD units (two centres; one did not have CAPD patients)

7.2.3 Analysis of interviews on policy protocols

The results include a summary of the information regarding the application of the National Access to Treatment Protocol (policy) in sampled units, and compliance at unit level with the Protocol.

All semi-structured interviews attempted to find answers to the following questions:

1. How does the [RRT] Programme receive its budget: nationally/ locally? (Budget flow)
2. What is the resource allocation policy and is there a defined geographical equity?
3. Was future expansion of the RRT network considered a priority among services and if so, how would the expansion support itself and is sustainability feasible?

7.3 Results from National Key Persons Interviews

The main aim of the interviews was to gather independent expert opinions on the national RRT programme, its resource allocation policy and whether it employed equitable means. Below are three quotes, all relating to financial resources:

"…The scope beyond calculating the average cost of the RRT patient is that it allows estimation of the next year's budget. If each centre allows for this, the final figures are to be presented by the director of the centre, along with other documentation, to the Ministry of Health having therefore a justification for obtaining their individual budget. Then, a national figure can be drawn for the entire Programme; money is the most important resource". **[I_3]**

"…The centres basically, do not receive individual budgets from a National Programme. While most centres provide these services along with those provided by teaching or district hospitals they will receive their annual budget accordingly, along with the historically set hospital's budgets…" **[I_4]**

"..While freestanding centres will receive their budgets independently (being registered as legal entities), units having had to provide inpatient care, will receive their budgets along with the Nephrology or Internal Medicine Department of the hospital they belong to; therefore it is a mixed budgeting…" **[I_5]**

Most interviewees did not answer the question on "equity" ("what is the distribution of resources, particularly budgets by centre?" and "what was the resource allocation policy and was there a defined geographical equity?**"**). One interviewee answered in relation to the Social Health Insurance Law recently passed through the Romanian Parliament:

"…as long as 7% of the National Health Insurance Fund is deployed to districts in order to balance equity in access to services, one assumes that 'wealthier' districts are willing to employ the same process within the ministry's annual health budget; however, it is more difficult to achieve this knowing that the health budget is small; the 'attitude' of these 'wealthier' districts will probably be to hold on to their budgets in order to improve services or to only maintain them at a certain quality, therefore allowing Renal units other options in order to improve their funding… …there were also some proposals regarding the 'channelling' of some financial resources from the health insurance fund towards the health budget of the Ministry of Health, namely a crude figure of 6-7 million USD for the RRT haemodialysis component [the term consumables was even specified what this money was to be used for]…" (as of April 1999 this non evidence based enforcement was still under debate at ministerial level). **[I_5]**

The RRT Programme receives a proportion of the health budget on an annual basis. The money to treat the RRT patients has been [historically] allocated to the Programme, regardless of the overall health budget situation; this had not changed by 2004. By 2007 the Programme appeared to be within spending parameters, but no one suitable was available to discuss this further.

Expansion of the RRT programme has always been a critical issue. This implies an increase in expenditure and while the budget is historically fixed, the Programme would have to look for this

type of resource elsewhere. However, the understanding remains that money was always required in accordance with the numbers of patients who were in stock in the previous financial year and multiplied by an estimated average cost. This was explored through the cost of illness Section in Chapter 6.

For the third question (Section 7.2.2) most interviewees addressed the structural changes needed for the renal services network. However financial issues were again highlighted:

"…as long as patients' transportation costs represent a 'good' proportion of their treatment cost, more smaller units have to be set up within a distance of no more than a 100 km distance from patients' homes, given the road infrastructure, etc". So far, "the difficulties encountered converge towards one single issue: the lack of financial resources". **[I_2]**

Other points interviewees made include the following:

Teaching centres have deployed some of their resources to neighbouring district hospitals within their catchment area. The idea behind this was that both patients and the other major stakeholders, providers and third party payer, received an efficient resource allocation. However, some of the issues under concern were beyond the aim of this research: e.g. national key persons were very unforthcoming with expert opinion as to what should happen in the Romanian RRT. Almost all interviewees referred to written documents such as the old access to treatment policies with comments such as "all the needed information is there…".

Nonetheless, all interviewees encouraged future research and changes in ways of decision making and priority setting. The clinical guidelines were dated 1991 and they were undergoing a radical review at the time the fieldwork was taking place. For example in the old guidance a capped age limit of 60 years old was set for acceptance on treatment and this was due to be changed to 70 years. The result of this change in policy has been a significant increase in the proportion of patients entering RRT above the age of 55 years, from 20% in 1996 to 32% in 2003, a 60% increase [122].

All three centre managers confirmed that the RRT policy has clearly taken up CAPD as the main safety valve in meeting treatment need and demand in Romania. Uptake on CAPD has been increasing after the first year since its introduction in 1995. Hospital HD remained the main form of RRT, but the proportion of those on hospital HD declined from 82% (1997) to 78% (2003) [122].

Financial resources appeared scarce in 1997, inequitably distributed, i.e. with no link to needs. For example, the network expanded very markedly since 1995, but the issue of transportation and distance from centre was still high on the agenda in 2003. This was despite reported outcomes on treatment apparently having improved, with survival above European reported figures. A mismatch in the efficiency of resource allocation raised further research questions, such as why has the network expanded to 71 adult centres and why only a fifth reported back on activity in 2003, similar to the number of centres which were providing RRT in 1997 [122; 215;217].

7.3 Secondary sources related to the national RRT policy & access to treatment

Access was granted to two key secondary sources of information in relation to the RRT policy at national level: the 1998 Annual Report of the Romanian Society of Nephrology, a national Charity and the National Access to Treatment Protocol [177;218].

The annual report contains achievements in relation to policy related outcomes, for example whether the acceptance or stock targets have been met and if so, by how much; however, in practice it was unclear from the report whether targets were achieved or not.

The National Access to Treatment Protocol was a dated national clinical guideline. Experts pointed out highlighted that a new one was being developed. By 2003 this was still not available for consultation, but a check with the second interviewee at the time suggested that the change made was that the age limit of 55 was lifted and no other age limit was set.

7.4 National clinical guidance and protocol for access to RRT

> "…this is a rather an old guideline, but is the only one in use; we [the Dialysis and Transplantation National Committee] are currently working on a second, updated, edition, which should be soon released, albeit for internal use" **[I_3]**

The 1991 National Guideline Document contains: general policy background for RRT; patient selection criteria for acceptance onto treatment; HD and access on this mode of treatment; CAPD and access on this mode of treatment; inclusion criteria (biological markers).

The general policy contains a Section entitled "Rights and entitlements" which lists social care issues associated with the renal patient. This guideline was not applied in practice, and the extent

of the implementation of these rights was not fully documented. No documentation of the pre-1989 clinical guideline and protocol was available in order to make comparisons.

7.5 Local interviews: local protocols on access to treatment

All local centre managers were medically qualified. The position allowed them to perform clinical and managerial tasks within one job role.

However, financial management was the job of an accountant. This was known as the Economic Director or Deputy Director, always deputising for the clinical or managing director on organisational matters. The clinical job attributes were usually delegated to either a consultant and/or the chief nurse.

Operational management was carried out by the chief nurse or nurse manager or Head nurse. Each treatment modality had one head nurse each. For the provision of hospital HD, each shift agreed upon someone responsible for operational management therefore the role of head nurse was delegated for that particular shift. These were usually the afternoon and night shifts.

A summary of the main points from local levels shows:

The national protocol on access to treatment served as a rough guideline; local rules and regulations were applied and most likely prevailed. Two of the local key persons were members of the National Dialysis and Transplantation Committee and both were aware of and working on the revised protocol; the third key person was not aware of the revision but did not seem surprised when they learned that it was in progress.

There were no written local protocols on access to RRT, whether pre-RRT care was included or even an early referral to a nephrologist when a CKD1 to CKD3 stage may have been detected, diabetes or hypertension diagnosed. The national Service Development Programme allowed centres or units to develop their own guidelines, flexibly around the national guidelines and the RRT policy. However, if access to RRT was not a critical issue, maintaining a patient on treatment could become a sensitive issue when provision with consumables which took over three quarters of the centre's budget, became critical. This might be the result of insufficient budgeting or changes in market prices or a bit of both; or, as and when at times the centre had a full capacity allowing a waiting list to develop with little flexibility of accessing treatment unless the patient

moved catchment area. Delay in start of treatment was not documented, nor were deaths due to such circumstances.

None of the local interviewees were aware of any budgeting decisions which took into account geographical (in)equities or other resource allocation criteria:

> "…budgets are approved as such and we make sure we get the supplies for some months while this money lasts; sponsors come along sometimes, they always did. The exchange rate of the LEI to the USD is another issue. Sometimes, the only difficulty that arises in money matters is the "additional" financial support which arrives from the government late in the year [second half of December]; it basically means that we cannot spend that money and it has to go back to the public budget…Then, this is counted as a non-spent fund. The paradox lies there; by the time the next year's public budget is debated the government decides: "we shall not increase the health care budget as they made returns at the end of last year". Basically each national programme encounters this difficulty and since the national health insurance law was passed matters have become even more complicated…the mass media have a major role in spreading such news, and inaccurate information leads to more confusion…"

At local level the national protocol is regarded as detailed and useful, but the sampled units use "local" variations of the national clinical guideline, for example:

- serum creatinine was interpreted as greater than 7 mg% and not greater than 8-10 mg%, which meant a lower threshold;
- while connective tissue disease (e.g. lupus nephritis) and diabetic nephropathy were excluded from the national protocol list of underlying causes of CKD, all three centres were accepting these patients locally, albeit not in big numbers;
- whereas a strict 5-6 HD initiation number of sessions/week was given by the national protocol, local centres had a more flexible RRT initiation policy and adapted initiation of treatment according to local casemix;
- it was difficult to document how the protocol was applied in relation to the real age-based inclusion and exclusion criteria for RRT;

- the definition of certain medical conditions had different interpretations at the at local level despite what the national protocol defined as exclusion criteria e.g. “psychotic symptoms”; locally this was interpreted as “psychoses” taken from psychiatric terminology and when patients were excluded from entry onto RRT;
- biological testing departed widely from the national guideline; particularly in the frequency with which they were carried out; local protocols often demonstrated that “there was no reason to perform a particular test as often as the national clinical guideline stated it (e.g. monthly, every 6 months, etc.);

7.6 Summary

The treatment policy was old and the new one was not available for consultation during the time the research was carried out. ERA-EDTA guidance was gaining more interest amongst an increasing number of centres and the National Renal Registry.

Local input into a national policy gathered momentum after 2000 and the age threshold is completely lifted.

By 2008, the administration of the RRT network laid the privatisation basis for 30% of centres.

By 2011, the entire RRT network operated under 100% private administration (similar to pharmacies).

Although out of scope, the public or private management of the renal network was not included in any of the discussions with policy makers. Inequity in resource allocation could inevitably be still recorded regardless of the network’s ownership.

A hypothesis could be formulated, in the sense that: the health care system’s “immaturity” (less than 15 years under current social insurance model), being under constant reforms and with an increased visibility of a political pressure for privatisation beyond RRT, leaves essential components such as universal access to good quality care behind. Policy issues were considered contextual in this research, but future recommendations include a greater emphasis on this aspect due to the high technology involved and due to the complexity surrounding acceptance on RRT, survival and quality of life at various points when under treatment.

8 The treatment model

8.1 Objectives

The broad objective of this chapter is to develop a treatment model for CKD5 under RRT and use it to help formulate policy recommendations for resource allocation in the context of estimated future needs for RRT.

The more specific objectives are:

- to calibrate the treatment model by fitting it to estimates of the stock of patients on RRT in Romania from the period 1996 to 2006; and
- to use it to estimate future stocks of RRT patients over the period 2007-2016.

8.2 Methodology and Methods

8.2.1 The structure of the treatment model for RRT

A patient's experience of RRT can be modelled as a number of changes of state. Some of these changes involve states of health (e.g. well, primary renal disease, end-stage renal failure, dead) and some involve the kind of care received (none, dialysis, transplant). In this model there are 4 states: RRT-HD, RRT-CAPD, RRT-functioning transplant and dead.

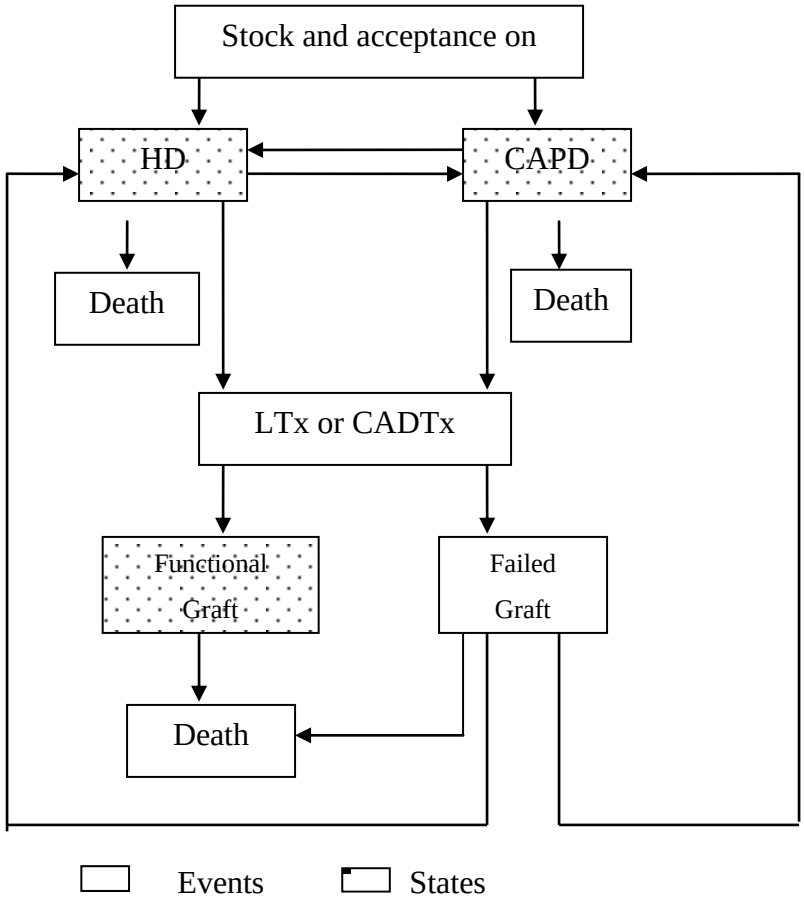
Over a given period of time, patients who start the period in some given state have certain probabilities of remaining in that state, or of transferring to some other state. A state transition model involves i) a set of 'initial conditions' (the numbers in each state at time zero) and ii) estimates of the probabilities of making the transition from each state to each other state in a given period. The set of these transition probabilities defines the transition matrix. Starting at the initial conditions, the transition matrix is applied repeatedly in a sequence of discrete time periods, and in this way the future behaviour of the system is simulated.

In this model new patients are 'accepted' into the patient pool and become prevalent patients (in stock) at the end of their first year of treatment. Patients accepted for treatment are initially put on either HD or CAPD. Subsequently they may switch between these modalities or receive a transplant at rates determined by the transition matrix. After a successful transplant a patient transfers to the functioning transplant state. After a failed transplant the patient can transfer to HD, CAPD or death. Each year, numbers of patients flow from state to state until they enter the

'absorbing' state of death [193;195]. Flows between states and events are indicated by arrows in Figure 8.1.The main model *output* is the distribution of patients across states at the end of each year.

In the calibration phase the model takes as data the annual number of new patients requiring HD and CAPD at the beginning of the period. Different values are then tried for subsequent acceptances and in the transition matrix to see how well the projected numbers in each state at the end of the period correspond to the observed values. In the projection phase, estimates of the numbers of acceptances each year are used and the model provides the projected numbers in each state in each future year.

Figure 8.1: Treatment model adapted for the illustration of the Romanian RRT



The model is adapted from Roderick et al and is implemented in Excel [60].

8.2.2 Data for the model

Initial conditions: The calculations begin with a total number of patients aged 15+ years across all types of RRT in 1997. This is based on data from all the centres which replied to both the EDTA and the Centre Questionnaire (Appendices 2 and 3) and the capture-recapture method (CRM) [229]. The proportions allocated to each treatment modality HD, CAPD and Tx are then either estimated from study data (Section 5.3, Objective 3 and Chapter 6, Section 6.2) or, for transplants, taken from the literature.

Transition probabilities: Initial estimates were based on study data or, for transplants, taken from the literature [60; 224]. The number of transplant patients at baseline was very small. Also the indications for transplantation (i.e. criteria for suitability) were not explicitly or publicly stated, and when these few patients had had their transplants could not be determined. However, as of 2006, the policy target was to achieve 250 transplants per year. This target matched the total number of patients alive with a transplant in 2003. It was not clear whether this target has been met since, but if it has, there would be a cumulative 500 patients by the end of 2004 and 750 by the end of 2005.

The treatment model allows for transitions between treatment modes, but these were not used in the analysis presented here; the necessary data on switching between HD and CAPD were not available, and switching from dialysis to a transplant was a rare and undocumented event in Romania [60].

8.2.3 The scenarios considered

Baseline acceptance scenario: This was set at 80 new patients per million and combined with 3 variants of mortality: a) a baseline value; b) a 50% increase and c) a 25% decrease.

Acceptance scenario 1 and variants: acceptance increases by 10% in ten years (an increase in the baseline of a cumulative 1% year on year) , combined with 3 variants of mortality: a) baseline value unchanged; b) a 50% increase and c) a 25% decrease.

Acceptance scenario 2 and variants: acceptance increases by 30% in ten years: combined with 3 variants of mortality: a) baseline value; b) a 50% increase and c) a 25% decrease.

Acceptance scenario 3 and variants: acceptance increases by 50% in ten years: combined with 3 variants of mortality: a) baseline value; b) a 50% increase and c) a 25% decrease.

Thus a total of 12 scenario variants were modelled, and these are summarised in Table 8.1.

Some of the reasons for considering changes in acceptance rate are that the prevalence of CKD may increase with improved detection of the syndrome itself, with ageing of the population and/or with an increased diagnosis of PRD and systemic conditions leading to it, most notably diabetes and hypertension.

One reason for considering variations in mortality was that the proportion of diabetic cases was not taken into account explicitly. However on the basis that diabetic patients would have a higher mortality rate, the high mortality rate scenarios were intended to represent situations with high percentages of diabetics. Thus the assumption made here was that scenarios with "high" mortality were consistent with an increase in the proportion of diabetic patients under RRT from the current 10% up to 30% (a third of stock). On the other hand mortality could decrease if quality of care improved, or if for some reason acceptances had less severe disease and/or fewer co-morbidities.

Table 8.1: Scenarios used in the treatment model.

Modelled stock/Assumptions	*Acceptance*	*Mortality*
Scenario 1a (baseline)	Baseline 80 pmp	Baseline 13% per year
Scenario 1b		Increased by 50% (19.5%)
Scenario 1c		Decreased by 25% (9.5%)
Scenario 2a	Increase of 10% in 10 years	Baseline 13% per year
Scenario 2b		Increased by 50% (19.5%)
Scenario 2c		Decreased by 25% (9.5%)
Scenario 3a	Increase of 30% in 10 years	Baseline 13% per year
Scenario 3b		Increased by 50% (19.5%)
Scenario 3c		Decreased by 25% (9.5%)
Scenario 4a	Increase of 50% in 10 years	Baseline 13% per year
Scenario 4b		Increased by 50% (19.5%)
Scenario 4c		Decreased by 25% (9.5%)

8.3 Model calibration (1997-2006)

Acceptance rates, both estimated and reported[122] from the same year by main type of iterative RRT, along with mortality estimates, were used as parameters to model ESRF for 10 years. For example acceptance rates in the 16 adult centres ranged from 11 to 85 pmp. Stock rates ranged from 119 to 169 pm, with one outlier at 222 pmp. Survivor probabilities from the three sampled units varied from 68% at 1 year to 84% at 3 years. Mortality rates after one year were 13% for HD, 5% for CAPD and 4% for transplant. (Transplant mortality was taken from the literature.)

In the baseline scenario, the 1997 starting stock was 78 pmp, and the acceptance rate 25 pmp.

On this basis the model suggests that total of 6,698 patients would have been in treatment by the end of the year 2006 (95% CI 6,602 to 6,887). The age-specific 15+ stock rate is 389 pmp (Table 8.2).

The figure for 2006 reported by the National Health Insurance Fund (NHIF) was 7,071, which is just outside the upper limit of the 95% CI for this baseline estimate.

In fact the best fit is given by the baseline scenario, with an estimate for 2006 of 6,698 patients in stock (95% CI from 6,602 to 6,887). The second closest result was scenario 4 (mortality unchanged and acceptance increased by 10%) with a figure of 6,978 (95% CI from 6,880 to 7,171).

Table 8.2: Results for 1997 to 2006: calibration and validation of the model – Baseline and 3 Scenarios (4x3 =12 combinations)

	Acceptance unchanged			*Acceptance increased by10%*			*Acceptance increased by 30%*			*Acceptance increased by 50%*		
	Mortality:											
	1 Baseline	2	3	4	5	6	7	8	9	10	11	12
Stock	Un-changed	Increased by 50%	Decreased by 25%	Un-changed	Increased by 50%	Decreased by 25%	Un-changed	Increased by 50%	Decreased by 25%	Un-changed	Increased by 50%	Decreased by 25%
1997	2,995	2,995	2,995	2,995	2,995	2,995	2,995	2,995	2,995	2,995	2,995	2,995
1998	3,645	3,311	3,819	3,645	3,311	3,819	3,645	3,311	3,819	3,645	3,311	3,819
1999	4,215	3,543	4,588	4,224	3,553	4,599	4,265	3,591	4,640	4,304	3,628	4,684
2000	4,715	3,715	5,310	4,743	3,744	5,339	4,859	3,843	5,465	4,981	3,948	5,592
2001	5,156	3,841	5,986	5,210	3,891	6,044	5,437	4,080	6,292	5,678	4,277	6,554
2002	5,545	3,932	6,617	5,633	4.011	6,710	6,003	4,303	7,129	6,405	4,623	7,577
2003	5,888	3,997	7,208	6,016	4,104	7,348	6,559	4,523	7,973	7,167	4,990	8,666
2004	6,191	4,043	7,760	6,365	4,185	7,949	7,114	4,742	8,828	7,973	5,384	9,826
2005	6,460	4,074	8,274	6,684	4,251	8,525	7,668	4,962	9.701	8,828	5,806	11,071
2006	6,698	4,097	8,755	6,978	4,310	9,070	8,226	5,187	10,589	9,742	6,263	12,407
2006 rate pmp	389	238	509	406	251	527	478	336	616	566	364	721
2006 reported	6,600	6,600	6,600	6,600	6,600	6,600	6,600	6,600	6,600	6,600	6,600	6,600

8.4 Model projection: 2007-2016

Having calibrated the first 10-year cycle against the 2006 reported stock, a further 10-year cycle (up to 2016) was projected under each scenario. The estimates are summarised in Table 8.3, with details in Appendix 11. The model projection scenario 4 for 2007 (6,978) was quite close to the reported figure for 2007 of 7,400 patients, implying that the 2007 figure is consistent with only a slight increase in capacity and little or no change in mortality [215].

Furthermore, from the point of view of the patient, the most optimistic scenario (scenario 12) suggests the following: if an increase in acceptance by 50% and a decrease of mortality by 25% are achieved then a stock rate of 721 pmp would have been recorded for 2006 and the projection for 2016 would have become 1,940 pmp.

The most pessimistic scenario (scenario 2) assumes that the acceptance rate remains unchanged, and that mortality increases by 50%. This gives a stock rate of 238 pmp for 2006 and an almost unchanged figure of 239 pmp for 2016. This scenario could arise if the stock of patients were to consist of an increasing proportion of the patients accepted having diabetic nephropathy and/or multiple co-morbidities (for example because they are older than current patients).

Under most scenarios, with current service provision, a total of up to 9,000 or 10,000 patients would be in treatment by 2016. This would be an increase of 40 to 45% in stock over the 2006 figure, reaching the rate of 526 pmp. If HD capacity cannot be increased beyond 2011 levels (70 centres), and the volume of transplantation remains limited, such an increase could only be achieved by substantial increases in the numbers of patients on CAPD.

The value of 526 pmp is close to the 1998 UK stock of 529 pmp (Table 2.3, literature review). This would also match the upper range of the reported European median stock rate of 579 pmp in 1992 [9]. Furthermore, in absolute terms the reported figure for stock in 2008 of 10,000 patients is closest to scenarios 3 and 6 (Table 8.3, year 2008).

Scenario 12 implies an increase in stock with estimated values of over 33,000 patients and a stock rate of 1,940 pmp. This rate is likely to be an over-estimate, as Japan and the USA have stock rate values around 1,000 pmp and health care in these countries appears to have met 100% of the CKD5 need on RRT.

8.5 Strengths and limitations

The treatment model has a number of strengths:

- it is the first model of this kind for Romanian CKD5 patients on RRT, and it is based primarily on Romanian data;
- at the heart of the model is the basic and well-known epidemiological equation: stock = acceptance x duration on treatment (prevalence= incidence survival);
- the plausibility of parameter values can be tested further with sensitivity analyses; and
- use of an Excel spreadsheet allows other scenarios to be easily investigated once the model is validated.

However it also has a number of limitations:

- survival in the model was not related to age. This is consistent with the literature [230]. Also there were insufficient Romanian data to estimate age specific rates. Overall 3-year survival was estimated at 68% (1995 cohort from the 3 centres), which compares with 60% survival in England (1997 cohort from UK Renal Registry reported in 2007 [230]). For context, life expectancy at birth is lower in Romania than in England, but the mean age at entry on RRT was much lower (modal age in Romania: 45 years, modal age in England > 60 years).
- likewise, no explicit allowance was made for effects of gender, or precursor conditions such as diabetes, or stage (CKD1 to CKD4) due to lack or unreliability of data.
- there were no Romanian data on transplants; and
- this simple model does not provide a platform for cost-effectiveness analysis.

Table 8.3: Results for 2007 to 2016: the projection period of the Model – Baseline and 3 Scenarios (4x3 =12 combinations)

	acceptance unchanged			acceptance increased by10%			acceptance increased by 30%			acceptance increased by 50%		
	mortality:											
	Baseline	2	3	4	5	6	7	8	9	10	11	12
Year and stock	Unchanged	increased by 50%	decreased by 25%	unchanged	increased by 50%	decreased by 25%	unchanged	increased by 50%	decreased by 25%	Unchanged	increased by 50%	decreased by 25%
2007 reported	7,400	7,400	7,400	7,400	7,400	7,400	7,400	7,400	7,400	7,400	7,400	7,400
2007	6,910	4,108	9,205	7,250	4,362	9,591	8,791	5,420	11,495	10,717	6,760	13,844
2008	7,097	4,117	9,624	7,501	4,410	10,087	9,366	5,664	12,424	11,770	7,301	15,391
2009	7,265	4,123	10,014	7,735	4,455	10,563	9,954	5,915	13,380	12,903	7,890	17,062
2010	7,414	4,124	10,377	7,954	4,501	11,016	10,556	6,181	14,365	14,126	8,533	18,867
2011	7,548	4,124	10,717	8,160	4,542	11,450	11,178	6,460	15,374	15,448	9,232	20,822
2012	7,667	4,123	11,034	8,354	4,584	11,868	11,819	6,751	16,420	16,881	9,999	22,937
2013	7,775	4,119	11,330	8,538	4,626	12,270	12,486	7,060	17,504	18,440	10,836	25,238
2014	7,870	4,119	11,603	8,715	4,668	12,654	13,170	7,383	18,620	20,126	11,748	27,727
2015	7,957	4,115	11,856	8,884	4,711	13,027	13,887	7,725	19,783	21,963	12,746	30,429
2016	8,037	4,111	12,094	9,046	4,752	13,380	14,633	8,082	20,986	23,956	13,836	33,370
2016 rate	467	239	703	526	276	778	851	470	1,220	1,393	804	1,940

Table 8.4 Summary of scenarios in the two periods: 1997 -2006 and 2007- 2016

	acceptance unchanged			acceptance increased by10%			acceptance increased by 30%			acceptance increased by 50%		
	mortality:											
Year and stock	unchanged	increased by 50%	decreased by 25%	unchanged	increased by 50%	decreased by 25%	unchanged	increased by 50%	decreased by 25%	unchanged	increased by 50%	decreased by 25%
2006	6,698	4,097	8,755	6,978	4,310	9,070	8,226	5,787	10,589	9,742	6,263	12,407
2016	8,037	4,111	12,094	9,046	4,752	13,380	14,633	8,082	20,986	23,956	13,836	33,370
2006 rate	389	238	509	406	251	527	478	336	616	566	364	721
2016 rate	467	239	703	526	276	778	851	470	1220	1393	804	1940

Although the effects of case-mix on survival were not included in the model explicitly, some indication of their likely implications is given by the use of variant scenarios, expressed as higher and lower mortality rates and higher and lower acceptance rates. In future modelling, the impact of changing risk factors on levels of disease should be incorporated more explicitly, with epidemiological and treatment models linked.

As well as population demographics (aging) and patient risk factors including leading conditions or precursors, local requirements for RRT will also depend on factors such as changes to catchment areas, and changes in policy on access to treatment perhaps reflecting changes in socio-economic variables and demand for care etc.

9 Discussion, conclusions and recommendations

9.1 Introduction

In this chapter results from each of the earlier chapters will be summarised and discussed, including:

- the burden of CKD and the prevalence of the main precursor conditions, in Romania and elsewhere;
- factors affecting need for RRT;
- the Romanian network of RRT services and its development;
- outcomes of RRT in Romania;
- data on costs of different forms of RRT in Romania; and
- the structure and validity of the decision-support treatment model.

Conclusions will be drawn, and suggestions made about possible lines for future research.

9.2 Epidemiology

9.2.1 Chronic Kidney Disease and its precursors

Chronic kidney disease is a complex syndrome. If left untreated, and kidney function deteriorates below a certain level (CKD5), it can lead to complications, accelerated progress of co-morbid conditions, and earlier than expected death.

There are many risk factors or precursor conditions for CKD, including primary renal diseases (PRD), diabetes mellitus (DM), hypertension (HT), lifestyle factors such as smoking, and also acquired and congenital immune-related conditions, or congenital and genetic disorders such as ADPKD (autosomal dominant polycystic kidney disease).

The limited data available on the prevalence of CKD5 (or stock for RRT) suggest that it is an uncommon condition in Romania. At least it was in 1997, when the estimated CKD5 rate in the national health survey was 1,222 pmp [163]. An earlier report of the Romanian Renal Registry gave a "prevalence rate of renal diseases" as 1,232.5 pmp with an annual "incidence" of 125 to 160 pmp [177]. There are no more recent Romanian data and only one English paper reports on a 1,700 pmp [151]. No other European country reports on this; neither has the National Health Insurance Fund nor the Ministry of Health through the Renal Committee, nor the Romanian Renal Registry have reported estimates for CKD by stages 1 to 5 in more recent years. However, some of the precursor conditions are highly prevalent in the general

population: hypertension for example, reaches a prevalence of 20 to 50% after the age of 50 years. Diabetes, predominantly type 2, reaches 4-8% in the adult population.

Also this is against a background of a Romanian population that has generally high mortality by European standards. According to WHO data, infant mortality and life expectancy in Romania have slightly improved between 1990 and 2006 [236]. (These indicators have the advantage of being regularly updated via Eurostat [170].) Nonetheless in 2006 life expectancy at birth was 73 years, which is still substantially less than, for example, France (81 years) or the United Kingdom (80 years). [237].

9.2.2 Rates of Primary Renal Disease (PRD) in Romania

The published PRD rate was 2.5% but the rate calculated for this study from the same dataset was 2.9%. This difference may be attributable to the use of different denominators; the denominator used in the reanalysis was the population aged 15 years and older, but it is unclear what denominator was used in the published rate. Another calculation, based on the number of PRD diagnoses/ population aged 15+, gave 3.03%, which is slightly higher as there were 298 PRD diagnoses in 283 individuals. These differences are small in the context of this study, but as a general rule the same inclusion and exclusion criteria should be used for both numerators and denominators.

In the reanalysis of the National Survey data [163], PRD was reported as the cause in 5 out of the 12 cases of CKD5 receiving RRT in Romania. This made PRD the most commonly reported cause, but the numbers involved are very small. More specifically, the 5 individuals with ICD-9 defined PRD and also CKD5 had the following: interstitial nephropathies, nephritic syndrome and prostrate hypertrophy which are also amongst the most frequently recorded PRDs in terms of percentage of population. Note though that while some PRD diagnoses are 'irreversible', (e.g. prostate hypertrophy complicated with interstitial nephropathy if the hypertrophy is not treated), some may recover, and then may or may not recur.. Perhaps a more important concern is that while in the developed or western societies the rate of PRD as an aetiological factor in CKD5 has dropped since the 1990s, possibly as a result of better treatment of streptococcal infection, this seems not to have happened yet in Romania [122]. This is despite a reported decrease in some form of glomerular disease, the MPGN [148].

9.2.3 Rates of hypertension in Romania

Hypertension is the most common of the precursors for CKD in the general Romanian population, but it does not necessarily affect the kidneys until late in life, typically after 50 years of age.

The substantial difference between the officially reported rates of hypertension in the National Health Insurance Fund data (6%) as against those in the National Survey Report (16.7%), and in the reanalysis of the e-dataset (14.7%) could be a result of poor case ascertainment in the insurance data due to inadequate description of the inclusion and exclusion criteria. Alternatively the figures based on the survey data may be over-estimates. The survey methodology included clinical measurements as well as self-reporting and if the coding guidelines are unclear, the results can be inconsistent. It is striking that the number of cases coded as hypertension in the survey dataset is greater than the number with recorded blood pressure measurements of ≥140/90 mm Hg. On one hand there may be over-reporting due to misclassified blood pressure readings, or un-validated self-reported hypertension. On the other hand it may be that effective management has brought high blood pressure down to within normal ranges.

Reported values from different parts of the country from other sources of data (National Health Insurance Fund and Ministry of Public Health) also vary widely, from under 3% to over 17%. However these prevalence rates are not age- or gender standardised in the smaller counties, and at least part of the observed variation may be attributable to differences in demographics, with higher prevalence in older populations. This could also be affected by variations in the amount of unmet need for treatment in older groups.

9.2.4 Rates of diabetes in Romania

Health data systems in Romania are weak, and this study sought to cross-reference estimates from different sources.

i) The National Survey, 1997.

The reported prevalence of diabetes in the National Survey was 3% [163]. However there were a further 12 cases in the dataset reported as having raised glycaemia levels but not coded as diabetes. They were possible impaired fasting glucose (IFG) tests, at a rate of 0.12%. These could have been "newly" detected (incident) DM cases, or possibly DM diagnosed but poorly treated, or non-compliant with treatment. These survey data give higher rates in older groups, but later (1998 to 2007) survey reports did not give age-specific rates.

ii) The Ministry of Public Health and National Health Insurance Fund (NHIF)

This source reported figures of 2.1% and 2.2% for 2004 and 2005 respectively, based on whole-population denominators. However, if a population denominator of people aged 15 years and above is

used, the 2.2% rate becomes 2.9%, which is closer to the 3% value measured in the 1997 National Health Survey.

iii) European Commission Report on major chronic diseases (EuroDiab Study[161]).

A slightly higher prevalence of diabetes of 4% was reported for Romania in 2007.

The estimates from sources i) and iii) were based on empirical data collection and nationally representative samples. The reported MoH and NHIF figures were estimates based on historical data for numerators (diabetes cases) and inter-censal population estimates for denominators.

The literature suggests that 25% of all diabetic individuals may develop chronic kidney disease within 10 years of diagnosis. (In one prospective Canadian study [56], all diabetic nephropathy cases eventually developed an impairment of the kidney function.)

One potentially important result from this study is the odds ratio of the diagnosis of chronic renal insufficiency in the presence of hypertension and diabetes together. In a calculation using data from the National Survey, an individual was almost eight times more likely to have chronic renal insufficiency when both diabetes and hypertension co-morbidities were present (OR =7.73). The numbers are small and the confidence interval very wide indeed (95% CI from 0.99 to 60.38), but this result is consistent with the literature.

9.2.5 Factors affecting the future requirement for RRT in Romania

One determinant of the numbers needing RRT is the prevalence of precursors and risk factors, and trends in these will affect future need. There have been increases in the prevalence of precursors or risk factors for CKD in Romania, be mainly in diabetes and hypertension, and these are expected to continue, in some scenarios by up to 82% (Table 3.10); indeed, Romania's diabetes prevalence may well grow to match that of western societies. Such increases in rates could be offset, but only to a limited extent, by the expected decrease in the country's total population (Tables 3.5 and 3.6), a decrease in smoking, and potentially a decrease in the prevalence of PRD.

A second determinant of the numbers needing RRT is duration of survival while on treatment. If survival improves, then the need for treatment capacity will increase even if acceptance rate is unchanged. However data on current survival (Section 9.1.4) are difficult to interpret. Three-year survival on RRT appears to be better in Romania than in England (68% vs. 60%), but age at acceptance for RRT is much

younger in Romania. One factor in this may be the lower expectation of life in Romania, and another may be past policies which excluded older patients from acceptance on RRT. With the expected increases in acceptance rates for older individuals, and the changing pattern of disease precursors (e.g. fewer smokers, more obesity and diabetes), current survival rates are an unreliable guide to what the rates might be in the future.

Early diagnosis of CKD may improve prognosis, and prevent or postpone the need for RRT. This may involve screening with e-GFR, with progression to later stages followed up with clinical check-ups. As of 2009, two surrogate markers are used to determine progress of CKD: proteinuria (the presence of proteins in urine, a highly sensitive marker of evolution towards diabetic nephropathy) and blood pressure.

Finally better management of precursor conditions will help contain population need for RRT. Effective treatment of high blood pressure and DM delays the onset of CKD 3 to 5. Good data on the prevalence of, and trends in, obesity, HT and DM will help in the prioritisation and targeting of the 'upstream' interventions essential to controlling the high and increasing prevalence of these conditions.

9.2.6 Evidence for unmet need for care for CKD

Unfortunately there were no direct data on levels of unmet need of CKD in Romania. For example in the National Survey there was no information as to whether any of the twelve individuals with chronic renal insufficiency were receiving renal replacement therapy, i.e. whether they represented a met or unmet need in terms of replacement therapy. They could have been on a waiting list for renal replacement therapy, but neither this nor their staging (1 to 5) was recorded in the dataset or the survey report. Thus for indications of levels of unmet need it was necessary to rely on indirect indicators. These are discussed in more detail in Section 9.3.5.

9.3 Services and utilisation

9.3.1 The economic context

In about ten years, from 1992/93 to 2002/03, the share of GDP spent on health care in Romania increased from 2.5% to 6%. This WHO-reported value should be treated with caution however given that it includes an increase of 100% in 5 years. This compares with a 10% average for the EU27 with further increases to come, and almost 20% for the USA (2010) at the time [236].

By 2000 the government was forecasting good long-term economic prospects and since 2002/03 the economy has been growing at a faster pace. By 2006 Romania was experiencing one of the highest rates of economic development in the Central European region, and unemployment dropped to 6% (4.5% in Bucharest). By 2010 unemployment had recovered to 1997 levels.

However over this period there were signs of emigration and depletion among skilled employees (in e.g. the building industry as well as among medical and nursing professionals) which only by 2008 had started to reverse.

9.3.2 The health care system: funding, legislation and the broader picture

The healthcare system is predominantly publicly funded and based on social insurance. New legislation would be required to allow new approaches to assessing quality of care alongside health technology and health economic assessments. However the legislative process is complex and in recent experience it takes time to draft laws, put them through consultation and pass them through parliament. Such delays also have an impact on population-based or targeted prevention health policies. An update of the healthcare system legislation is overdue.

Social insurance premiums, through which the system is financed, fell from a proportion of monthly salary of 16% in 1998 to 12.9% in 2008. The 12.9% is made up of an employee's contribution of 6.5% and the employer's contribution of 6.35%, of which 0.85% is a "sick leave" component. Despite sustained improvement in the level of contributions to the NHIF, such as better coverage in premium collections, the system remains short of funds.

Since 2010 hospitals and other large service providers have come under the control of local authorities and councils. Medical staff and nurses are employed by the National Health Insurance System. Professionally, staff are accountable to the College which has representation at local level (counties + Bucharest, capital city). Renal tertiary services are largely provided privately, while continuing to be funded publicly.

Romania needs a clearer health planning process, and better mapping of care pathways from prevention to tertiary care. Some programmes, such as vaccination and immunisation, must have their resources ring-fenced; others could be more efficiently and effectively provided if their provision and supply were guided by needs assessments.

9.3.3 The RRT network

By 2007 only eleven health care programmes out of thirty remained the direct responsibility of the Ministry of [Public] Health, the national renal replacement therapy programme being one of them. (Another was control of diabetes which has become a priority programme since 2006.)

From 2007, annual operational budgets have been established via the National Health Insurance Fund, through its "sub-programme" components. The eleventh budget entry is "renal replacement therapy for end-stage renal failure". Budgets for each centre are based largely on the annual average cost/ patient of HD and of CAPD and on a historical basis.

The number of RRT centres in the country more than doubled between 1997 and 2003, from 30 to 70. Ten percent of the centres were privatised in 2007, but these included some of the larger ones, so that in 2008, 36% of RRT patients were treated in private centres. This compares with reported figures of e.g. 75% in Czech Republic, 85% in Poland and 90% in Hungary. In Romania most of the provider contracts involved Greek partners [234].

By 2011 the provision of tertiary services for RRT was entirely privately operated, with teaching units and district units distributed throughout the country. Not all districts provide RRT and some patients have to travel substantial distances to the nearest teaching unit.

According to the Nephrology Committee of the Ministry of Health, complete privatisation would address the lack of transparency in policy on acceptance for treatment, by lifting the age threshold. However privatisation is likely to make access to information for planning and evaluation purposes even more difficult, particularly in terms of costs and where they fall. Market-fixing or "patron-client" mechanisms have been a feature in this medical field in Romania. (This study could not address aspects such as "under-the-table" payments, a phenomenon close to the "take there, give here" described by those who studied this concept which is very deeply rooted in some societies [238]. For example, none of the published reports [122, 177] explain the observed geographical inequalities.)

In relation to staffing the most recent available figure for generalist nurses/100,000 population for Romania is 830 for 2002. It is believed that numbers of general nurses and the ratio of nurses to 100,000 population in Romania did not change materially between 1990 to 2002. For comparison, the European (EU15) average figures were 829 in 1997 and 990 in 2002, but some developed countries had more than 2,500 nurses per 100,000.

The 1996 report of the Romanian Society of Nephrology reported 447 dialysis nurses working in 27 centres in 1995, giving an average of 2.6 patients/ RRT nurse. In 1997 there were 27.1 fte RRT specialist nurses per million population (pmp) for the 14 centres which reported on staff resources, If the stock estimate is at 139 pmp, as reported for that year, this gives 5 patients/ RRT nurse. By 2003 this ratio may have increased to 6 or 7 patients/ nurse, but this is only an estimate based on changes in reported stock and an unchanged number of specialist nurses.

Despite the substantial increases in the number of RRT facilities in Romania the number of specialist nurses remains below the European average according to the Romanian Society of Nephrology.

9.3.4 Estimates of RRT 'stock' in Romania.

As in section 9.2.4, this study involved cross-referencing estimates or triangulation from different sources and reports.

i) The renal registry

The official national 'stock' rate for CKD5 on RRT was reported as 250 pmp in 2003 with earlier values of 19 (1991) and 57 (1996) pmp. The latest figure can be compared with the corresponding figures for England (529 pmp), and the European median (437 pmp) .

ii) The EDTA-ERA

A 127 pmp stock rate was reported for haemodialysis (HD) for Romania to this source in 1998 [223]. The overall RRT stock rate, including transplant and CAPD patients, was reported to the same source as 139 pmp[2278]. Further information was requested from the EDTA-ERA in 2008 but was not available.

iii) The Society of Nephrology

In data from the Society's published report for 2004 it seems as though there is a reassuring correlation between time series for stock and number of centres: stock rates increased from 55 in 1995 to 127 in 1997 to 250 for 2003, while number of centres increase from 22 to 30 to 70 in the same years. However these figures are based on diminishing numbers of centres reporting to the Society: 22 in 1995, 18 in 1997 and 14 in 2003 [122].

iv) This study: data from the Centre Questionnaires

The present study involved making an independent estimate of the stock rate using data from responses to the centre questionnaire and from the EDTA. In the 3 responding centres the stock rate was estimated

at 112 to 119 pmp with centre rates varying from 32 to 222 pmp. The capture-recapture method (CRM) was used to deal with the incomplete coverage of facilities. On the assumption that there was a high degree of independence between the data from the responding centres and data from the EDTA, it was estimated that the national stock rate in 1997 was 161 to 175 patients per million.

This estimate is subject to three limitations. One is that because the stock of 616 patients common to the EDTA and the Centre Questionnaire were not identifiable by age or gender, no age/gender breakdown could be provided for the national estimate. Second, primary questionnaire data were limited to only 3 units and these may not reflect the national picture. And third, case ascertainment in the responding facilities may have been incomplete. Nonetheless, both estimates are of the same order of magnitude.

v) National Health Insurance Fund estimates

In more recent years the NHIF has reported estimated stock levels of CKD5 under RRT as 6,600 patients in 2006 and 7,400 in 2007, and it was predicting a figure of 10,000 patients for 2008 [215]. The NHIF reported numbers rather than actual rates, but their numbers suggest CKD5 stock rates of: 382, 428 and 578 pmp in the 15+ population.

9.3.5 Indirect estimates of unmet need

How do these figures for stock of patients receiving RRT compare with estimates of the prevalence of CKD5? The 1997 National Survey gave an estimated prevalence rate of 1,222.5 pmp (section 9.2.1). Taken at face value, and subtracting the various stock estimates of around 150 to 500 pmp, this suggests a very high level of unmet need, of around 750 to 1000 pmp requiring RRT or other nephrological care but not getting it. What could be the reasons for such a large difference? (Note that the base years for these estimates differ - 1997 for prevalence of CKD5 vs 2003 for RRT stock. However the expectation would be for CKD5 to have been going up, not down.)

It is quite likely that the figure for CKD5 from the National Survey is an overestimate of the true need for RRT. It was seen that other countries in Europe have stock rates of about 500 pmp; only the USA and Japan have ever reported figures close to 1,000 pmp and these rates have plateau'd, suggesting that needs are largely being met. The number of cases in the survey was small (n = 12) and so the confidence intervals were wide (660 to 2,200 pmp). Also a proportion of patients receiving RRT will not have been counted as stock because they will have been in treatment for less than 90 days. It is possible that some patients were considered inappropriate or contraindicated for RRT; and some patients

may have been unwilling to accept treatment. Even in developed societies patients may wait too long for a transplant if that this the only practicable modality, and a proportion may die without their needs for RRT having been met.

Thus although there is considerable uncertainty about the figures, it does seem likely that there is a residual gap between prevalence of CKD5 and stock of RRT in Romania, indicating unmet need.

However these stock figures are of limited value for planning purposes. First, they do not distinguish between incident and prevalent patients (or newly accepted and currently in treatment). If the acceptance rates were known, it would be easier to plan for the required capacity. Then there is the related but different question of the number of centres required. The location of these centres will need to be such as to provide equitable access, conditional on affordability and the optimum treatment modality mix. It also seems likely that this gap between need and supply will be subject to substantial variation in terms of other factors such as gender and age. While inequities are at the core of healthcare public health, providers of RRT tend to be only secondarily concerned with equity; clinical matters come first.

9.3.6 RRT stock with HT and DM.

The proportions of precursor conditions in those on RRT in Romania differ from the proportions recorded elsewhere, with almost 85-90% of CKD5 on RRT in Romania still due to PRD. This has been reported in EDTA annual reports and published articles[110; 122; 227]. It may be that while in western societies needs for CKD5 on RRT due to a primary renal disease (PRD) have been met, and treatment has then been extended to the other predominant underlying conditions such as hypertension (HT) and diabetes (DM), in Romania this has yet to occur.

There are a number of other possible explanations for the small proportion with hypertension as the precursor condition in Romanian RRT patients. One could be that in some cases HT develops concurrently with the early stages of CKD; this is known as the renal "compensatory" mechanism for the loss of kidney function, or secondary HT. The loss of kidney function could be shown only by the asymptomatic decrease in GFR in stages CKD1 and 2[56; 58; 68; 93; 113; 119; 185; 227] . Alternatively, if the CKD stage is not established in a patient with HT until much later in the progression of the CKD, for example through a late referral, then there are questions about what ICD codes might have been used: whether primary HT with kidney complications or primary CKD with secondary HT. The latter type of coding is

much more likely for the Romanian CKD5 patient who might not reach the point of a referral for nephrology because another vascular complication of raised blood pressure has come first, such as a cardiac event (e.g. a myocardial infarction) or a cerebro-vascular event (stroke). However it is striking that in the data from the three sampled units reported in Chapter 7, the modal group in the age distribution of RRT patients was 35-44 years, followed by group aged 45-54 years. Thus in 1997 the Romanian patients were much younger than their western peers, and below the age at which hypertension becomes most prevalent. This was still the case in 2003 [122; 177]. The younger the cohort of patients, the less likely that: 1) HT is an underlying CKD precursor and 2) the treatment needs for the older CKD patients are being met. This could reflect inequalities in provision or acceptance policies related to age. However more recently, treatment policies have been reviewed and the age threshold has been lifted (see section 9.3.3).

In the UK in 1970, 2% of those on RRT had diabetes as the underlying cause, and the figure for Romania in 1991 was very similar at 1-2%. Now a quarter of the UK renal replacement therapy treated population has diabetes as an underlying cause. By 2003 the proportion in Romania had also grown, but by much less, to 10%. However, the calculated PAR% suggests an estimated figure of 30.5% for Romania, implying a large difference between sources in the proportion of acceptance with DM nephropathy. This could be either due to a lag in the occurrence and/or detection of diabetic nephropathy, to diabetic nephropathy patients not yet actually requiring RRT, or to diabetic nephropathy patients accessing RRT late in the progression of their disease and not surviving much into the 'beyond 90 days of treatment' cohort. Scenarios for the evolution of DM nephropathy could include: a) physiological changes are reversible in DM patients, e.g. better prevention of vascular complications and DM nephropathy will not reach western levels or b) these changes are irreversible, and DM nephropathy will follow the epidemiology of western society. Whichever the direction, the proportion of those on RRT needs monitoring to see if this increases or stays at 10%. The % with PRD and HT may change even if the RRT stock rate plateaus. However it seems likely that DM will become the leading precursor condition for chronic kidney disease and end-stage renal failure in Romania very soon if the epidemiology of the condition follows its expected course.

One further explanation for RRT patients in Romania having a different mix of precursors to those in western societies is late referral to a nephrologist. The argument is that late referrals (at a later CKD stage), combined with the younger age of the Romanian RRT patient, leads to poorer outcomes and a

shortening of the duration on treatment. In a large cohort Scottish study by Marks (2012) it was found that the relationship between RRT initiation and all cause mortality is an important parameter for planning RRT, regardless of the age of the patient. In this cohort, patients initially had CKD stages 3b, 4 or 5 (66% were stage 3b), and after a 6-year follow-up only 5% had started on RRT; 59% had died without any RRT, and 36% were alive and had not started RRT, suggesting that CKD develops slowly in the later stages, in older patients. They also showed that the probability of starting on RRT decreases with age, but the actual numbers increase. And third, they found a higher individual risk of all cause mortality at younger ages when compared with peers in the general population (mortality rate ratios or RR), but higher numbers of deaths (attributable risk or mortality rate excess) in older patients, latter being expected [155].

There are several possible reasons for this. There could be a greater contribution to mortality from premature cardiovascular disease and non-traditional cardiovascular risk factors in the young than in the elderly; 40% of patients had ischaemic heart disease at baseline. Another explanation could be renal pathology, i.e. younger people with CKD may progress faster than elderly individuals and there is probably more use of conservative care among those greater numbers of elderly with CKD [155]. When some patients are referred late to specialist care, RRT capacity may be full and starting on treatment further delayed. Some patients never reach specialist care until very late because of primary care "ignorance" or misdiagnosis. Some patients may not bring their problem to the attention of their GP, or even visit the surgery for e.g. routine BP measurements.

The scale of problems of this kind can be reduced by introducing clinical pathways for secondary prevention of CKD, including pathways for treatment of diabetes and hypertension. The UK has developed such pathways, for example, with the use of ACE inhibitors in the treatment for hypertension, but also in assisting with a slowdown in proteinuria, and thus a slowdown in CKD progression towards stages 3 to 5. Such findings, backed up by epidemiologically supported tools such as relative vs. absolute risks, are endorsed by established UK public health renal researchers [8;44;56;60;151; 155; 174;180].

9.3.7 RRT acceptance

In terms of acceptance rates, the only primary data were from the centre questionnaires. Rates from each of the 14 responding centres varied widely from 11 to 85 pmp per year. The lowest value came from centre 2 which has the largest catchment area and the youngest demographic profile in the country (its

stock was also lowest at 32 pmp; this centre separately reported also on a 10-year renal biopsy results with annual rates of 11 pmp/year and a proportion of 10% of cases being diagnosed with CKD, but no staging was reported [148]). The highest value of 85 pmp was from a north-western centre with a small catchment area and a relatively old demographic profile, similar to the population in centre 3. For comparison, the European median value is 79 pmp (1992). The latest UK figure from the UK Renal Registry gives 110 pmp (by 2012 called 'take-on rate' instead of acceptance). These acceptance rates proved difficult to reconcile with the national estimate of 127 pmp as "national 3-year rolling average of CKD all stages" in 1996 [177], unless this was a one-off 100% take-on rate for that year which is not possible. The registry report went on to say that "the assumption for requirement is 65 to 75 pmp per year, given that the UK has a 78 pmp acceptance rate". These figures were reported by the Romanian National Renal Registry without a reference in 1996. However a report for 2003 gives acceptance as 128 pmp, still higher than the 110 pmp UK Renal Registry reported figure [160; 227].

In this research, the variation in acceptance rates from 11 to 85 pmp suggests a) geographical inequity in distribution of resources or, b) a genuinely higher requirement in the western part of the country where the population is "older" than in the east. A combination of the two explanations is possible and merits further investigation. However, numerators and denominators must be clearly defined by catchment area and national level estimates need to be more rigorously determined.

9.3.8 Treatment modality within stock and acceptance

The great majority of patients start on HD or CAPD. In Romania, the majority (over 80%) received HD as the main modality of treatment [160; 122; 163; 177;227]. CAPD was introduced in 1995 but it was not until after 1998 that it became more established in Romania [222]. Primary data collection for this study ended in 1998 and trends in modality beyond this date were not available from other sources.

9.3.9 Costs and budgets

For 2007, the year prior to privatisation of a third of RRT network, a budget of €93 million was reported with no overspending (expenditure accounting for 98.1% of the budget), with a similar budget for 2008, except that €14.5 million (15% of the budget) was ring-fenced for HD equipment purchased in newly privatised centres. Also in 2007 average costs were reported by the NHIF as: €19,510 for hospital HD and €13,135 for CAPD. It is difficult to make independent estimates for these figures based on e.g. cost per session and number of sessions per year, not only because of shortage of data on costs and rates but

also because of exchange rate fluctuations and the unpublished costing methodologies used by the Ministry of Health (MoH) until 1998 and NHIF thereafter.

Reported figures have shown a substantial difference in the cost of HD per patient per year between state owned centres and privately run centres. In 2009 these were €11,000 and €18,400 respectively [215]. During this period there was a substantial drop in the cost of HD in state owned facilities, whilst private centres provided services at costs similar to those reported prior to privatisation. However, these figures were at odds with reported costs per dialysis session, quoted by the same source as €118 in a private centre and €128 to €148 in a public centre. The difference may be explained through cash flow mechanisms and the inclusion and exclusion of some costs, or possibly by fewer sessions per patient in the public sector.

For haemodialysis patients, the costs of treatment of renal anaemia were excluded. This was due to poor data on costs of EPO (hu-EPO, genetically recombinant erythropoietin). EPO is very expensive and it is not supplied to centres on a regular basis as there is no budget to cover it. Some patients pay out of pocket for its procurement and administration. The potential use of it in the treatment of renal anaemia was tested in 1995 when EPO was received through donations, and 15-18% of patients benefited for a 3-4 month series of treatment. At the time of the fieldwork of this study the treatment of anaemia was still carried out with PRBC volume (packed red blood cells). No information was available on the effects of using EPO, except a reduction in risk of blood-borne infection.

The cost-effectiveness analysis (CEA) carried out as part of the present study showed that slightly better effectiveness (survival) might be achieved under centre haemodialysis but probably at a greater cost. Studies elsewhere have found that transplantation is the most cost-effective modality, but transplant costs were not documented for the first year post-transplant, and so no such comparison was possible using Romanian data.

The 1997 figures can only serve to focus research questions and formulate hypotheses. For example, it may be the case that HD appears to be slightly less cost-effective than CAPD in Romania; however, this needs further exploration, to include elements of treatment access, centre capacity, point in time of referral (stage of condition, etc) and quality of care post- access. These variables should to be taken into account when calculating life years gained on each treatment.

9.3.10 Treatment outcomes

Survival and quality of life are the usual measures of outcome in renal patients. Because of the limited time for data collection and lack of possibility of follow-up of patient morbidity, this study focused on the measurement of 3-year survival which was 68%. The other important finding was that the presence of diabetes may not influence survival on RRT in Romania, at least not in the short term (in the estimates with follow-up of up to two years).

The number of centres providing data for the survival analysis was small (only 3) and extrapolation of the results to the entire renal population on RRT for the given cohort involves strong assumptions. Also the number of patients sampled from each centre was not large enough to detect anything but gross differences in outcomes between HD and CAPD. For outcome measurements to assist modelling and planning, longer periods of follow-up and larger samples are needed in order to assess the impact of morbidity and co-morbidity over five-, and maybe ten-year periods[233]. In England for example, survival rates have been estimated for up to 8 years of treatment[232] (60% for similar pre-2000 patient cohorts, in patients older than the Romanian patients [122]).

Reported survival in Romania was better than the European average in 2003. This was surprising in view of the Romanian acceptance and stock rates, which reportedly lagged behind most European countries. One explanation is that the almost 600% increase in facilities/centres and 700% increase in dialysis machines during the period from 1991 to 2003 led to an increase in one year survival because this expansion in capacity[110,] led to an increase in acceptance rates including less severe patients, and hence a less severe case-mix among the patient stock[163; 177]. Other explanatory factors could be that the Romanian patients are younger than elsewhere, and there may be some advantage in newer equipment[114;155; 174].

With regard to quality of life, only two Romanian RRT studies published in the literature provide a baseline data on this, which is an insufficient basis for policy making and planning. QoL data are best derived with a prospective study design with QoL measured at baseline (i.e. at entry to treatment), and then at one or more follow-up points, at 6 months and/or 12 months say. In both the Romanian studies, scores were calculated at the start and end of a limited study period after an "average of x months of follow-up" with a period prevalence cross-sectional application, to both newly accepted and patients in stock, of the SF-36 at two points in time. There was no distinction between newly accepted patients and patients who had been on RRT for some time, so the methodology cannot take into account any "lead

time bias"[142, 143; 147.] All three studies (two having used the SF-36 and one the KDQL) used the same general population norm, established much earlier, during SF-36 validation studies in the Romanian general population in the mid-nineties; the KDQL seems to have benchmarked results against the SF-36 norm [147].

Benchmarking quality of life scores for RRT patients in both these published studies against scores for the Romanian general population showed little or no discrepancy despite the different location and different years when the studies were carried out. In both Romanian studies QoL for haemodialysis patients was slightly worse than that observed in the general population. These Romanian surveys provided no results for transplant patients.

Research with appropriate benchmarking in the UK and the Netherlands has also shown that quality of life differs little between transplant patients and the general population. Other differences, e.g. between HD and CAPD, have been noted, but some of the differences are statistically significant and others not.

9.3.11 RRT policies

The qualitative component of this study included exploration of national and local treatment policies.

As has been described in section 9.3.2, the health care system changed in 1998 to a social insurance model, but the delivery of RRT did not really begin to change until ten years later when 10% of services were privatised. Primary data collection for this study ended before then. At that time there were two possible sources of data on policy: the National Renal Registry and the Annual Report of the national dialysis and transplantation committee at the Ministry of Health. Ministry reports are generally inaccessible to the public or scholars.

Local centres were supposed to have been guided by the 'old' (1991) national protocol until 1998, and this involved an age 'limit' of age 55. However in practice they also followed local rules and regulations. Thus the age threshold began to be lifted at the local level in the early 1990s, as confirmed by the local key persons' interviews.

The national dialysis and transplantation committee was updating the access to treatment protocol at the time of the primary data collection in 1998. The major point addressed was the age limit, which all units agreed to increase to at least age 70, although most chose no upper age limit; that was also in line with a documented increase in the uptake of older patients. Treatment protocols were limited to acceptance criteria, with nothing explicit on process or outcomes.

Transplantation was not covered in the 1991 guidelines. The Law of Tissues and Transplantation was passed by Parliament seven years later (1998) and this referred to general organ transplantation of which kidneys were included along with cornea, pancreas, etc. The reference to kidney transplantation was for living related transplantation only; reference to cadaver donors was added later in an amendment to the Act. In 1998 two centres were performing transplantation and as of 2003 another two were set up. However information on renal transplantation policy was not available and the only information was obtained via EDTA-ERA reporting [108; 110; 126; 133; 227].

One element missing from this study was a thorough assessment of the extent of inequity in the delivery of RRT services in Romania. Gender differences and geographic variations in acceptance and stock were the main inequalities observed. The association between smoking and CKD may partially explain the gender inequality on RRT, with higher smoking rates in males than females, regardless of location. The apparent geographic variation could be explained, in the absence of comparisons based on standardised rates, by the older population living in the western part of Romania as documented in Ministry of Health chronic disease reports.

9.4 Modelling

The stock estimate obtained from the CRM of 173 pmp, with 95% CIs of 169 to 175 pmp (Chapter 8) was used as the baseline, with 11 other scenarios for the treatment model, i.e. 2,995 patients in a population of 17.3 million-population over 15 years.

The model was calibrated by comparing different acceptance and mortality scenarios over a ten-year period and comparing the final stock with the 'observed' figure. On this basis a plausible set of scenarios for acceptance and mortality rates was identified. However, the parameters used in these scenarios are crude and need to be further improved, for example either by refining the existing parameters (e.g. age-adjusted mortality or survival), adding new parameters such as diabetes and non-diabetes CKD; and/or by disaggregation, eg by gender, if gender inequalities are to be addressed.

Although the 2003 report suggests improved treatment outcomes (with 1 year survival near or above European average) the role of improved outcomes may not be properly reflected in the modelling, whether in the first period of validation, or in the projections. The estimated stock with improved outcomes (mortality decreased by 25%) gives values of around 9,070 patients for 2006 and the reported

figure is significantly lower. (A stock of 9,070 patients implies a stock rate of 527 pmp, closer to the European average of 579 pmp [151]).

The model would be improved by adding intermediate states, such as various stages of the disease in the case of precursors, particularly hypertension and diabetes. In the case of hypertension the international classification defines these different stages and in the case of diabetes, the pre-diabetes stage (IFG stage) is distinct from an established diagnosis, which can be disaggregated by duration of disease (1 year, 5 years).

Pressure on services due to aging, and the issue of age-related treatment thresholds will undoubtedly reoccur during Romanian demographic transition to a more elderly population. However, as found by Scottish researchers the contrast between relative and absolute risk for both RRT initiation (acceptance or take-on rate) and age-specific mortality illustrates the difficulties for planning services [155; 174]. As we have seen, any age-related restrictions on access to treatment were lifted in 1999, but during calibration and the next cycle of the model a few scenarios match currently reported number of patients in RRT. On the plus side this makes the model a good starting point.

Equity (in terms of variation in utilisation or access by geography, ethnic mix, age, socio-economic factors, gender etc) is not currently an explicit factor in treatment policy, nor is how to improve accessibility in a private service in relation to such factors [122]. Further monitoring through epidemiological research could improve information in this area and assist in reducing inequalities if that were considered important. Such parameters could also have an impact on the projections and should be modelled.

9.5 Conclusions

The research question for this study was: how might epidemiological and health care systems data be used to inform the planning of services for renal replacement therapy in Romania?

From national health survey trends it appears that the prevalence of many of the precursor conditions for CKD has remained reasonably constant. The exception is diabetes, and given the time lag before diabetic nephropathy evolves into CKD5 it seems reasonable to expect a substantial increase in the requirement for RRT associated with this condition. The PAR% suggests that with a 4% prevalence of diabetes in the general population, the proportion of diabetic nephropathy on RRT would be expected to be close to 30% of the case-mix, whereas in Romania the reported proportion was only 10% in 2003.

The information reviewed and obtained through interviews on health care effectiveness, provision, policies and guidelines remained insufficient in allowing for the description of some of the quality aspects of the RRT services. For example, the effects of the transition from public to private management of the dialysis network were important but beyond the scope of this thesis. As a result the treatment model included only clinical and epidemiological rather than health care system parameters. Further development could incorporate policy elements.

The treatment model has a simple design; it is based on a spreadsheet model which can be easily used for planning service purposes and can also be further developed. Calibration and validation was carried out over 10 years. The model explains crudely how the stock of patients varies with fluctuations in acceptance and clinical outcomes (mortality or survival on RRT). Due to the wide range of scenarios used, some fit the treatment requirement which in turn could be translated to meeting treatment needs as long as treatment remains affordable. However, the fluctuations in the prevalence of condition precursors, or future trends, need to be further modelled with an epidemiological model. Good quality epidemiological information will improve the treatment model.

In this study an attempt was made to estimate treatment costs using a standard set of methods. This was complicated by the lack of standardisation in administrative data collection and reporting at the local level. For example in some areas overhead costs included salaries. Transplantation costs could not be directly measured and so the cost-effectiveness analysis was limited to dialysis. And finally because of the small samples available from the responding centres, the cost-effectiveness of HD vs CPD could not be reliably established. Yet these data are needed for service planning and budgeting.

The conduct of the study was hampered by policy turbulence: RRT treatment policy was changing within a continuously changing health care system, as the service delivery and organisation of the RRT network became privately managed.

One strength of this study lies in its search for, collection, and use of Romanian data. Another is its use of scenarios consistent with these data in the calibration of the spreadsheet-based treatment model. The methodology is generic, and if the second cycle is validated the model can be used for further planning in this service area.

At the same time the use of Romanian data is a major weakness, with questions about its validity, especially of the data from secondary sources. Primary data may also be subject to hidden measurement

bias, for example around diagnosis coding at registration; and misclassification as well as missing values may have also hindered the information quality. However, the international literature made possible many comparisons.

The information base for this decision-support modelling exercise was weak mainly due to incomplete data, such as transplantation data or the impossibility of measuring more than one clinical outcome such as quality of life. The greatest aid came from using complementary epidemiological tools and methods: the population attributable risk percent (PAR%) estimate for cross-checking with the proportion of diabetes on RRT, the impact fraction (IF) for estimating levels of acceptance on RRT (incidence), and the capture-recapture method (CRM) to improve the quality of the stock (prevalence on RRT) estimate.

Overall, there appears to be under-provision of care for CKD5 in Romania, particularly for diabetic nephropathy.

9.6 Recommendations for further research

9.6.1 Epidemiological research needed

One part of this study was concerned with estimating the burden of CKD, now and in the future. Epidemiological studies of CKD and its progression through stages CKD 1 to 4 may give further insights into disease progression towards CKD5. It was clear that estimating the future burden of CKD will also depend on better data on levels and trends in the burdens of hypertension and diabetes, and a better understanding of the implications of changes in these for CKD.

For example in the estimates made for this study, disease factors or precursors were assumed to be acting in isolation. Interactions, whether competing and compounding, were not taken into account, and these merit further attention through long-term cohort studies. Also multi-centre and cross-national samples would improve the power and representativeness of findings.

Another priority for epidemiological research in Romania is the use of more appropriate comparisons, i.e. with countries of similar socio-economic characteristics in the region, and with adjustment for known confounders, e.g. by using standardised rates to adjust for differences in age structure. Comparisons using the data currently available are very difficult to interpret, either due to little information on definition of cases, numerators and denominators or due to ambiguous use of terms (ESRD, ESRF, CRI and CKD). This proved particularly difficult when comparisons were attempted with data from former communist countries.

A role has been identified for development of primary prevention strategies to prevent or delay the development of hypertension and diabetes, and hence of CKD. Also there are complementary roles for secondary prevention to control existing diabetes and hypertension, including better compliance with treatment, especially in the case of the hypertension. However the implications of more effective strategies in these areas for quantitative estimates of the future burden of CKD are not clear, and more sophisticated epidemiological models are needed for this too.

9.6.2 Specific factors that affect disease progression and outcomes:

There are many factors which affect the progression and outcomes of kidney disease. *Patient-related* factors include age, precursor conditions, and type/severity (staging) of CKD. Socio-economic status may be used as an indicator or correlate of a variety of more specific life-style and environmental factors. Data from different geographic areas can provide 'natural experiments', in which variations in risk factors can be related to variation in outcome.

Service-related factors would include: geography and access, type of facility and e.g. delayed referral. Research questions could include: is access/acceptance on RRT based on requirement, need or other factors such as public vs. private provision. Geographic equity may need to be considered for local planning purposes and should be a matter for future research. Studies of the impact of time to referral on outcome could also provide valuable insights.

If this kind of information is to become really useful for future service planning, and if factors such as gender, age, cancer and diabetes are to be taken into account when updating policy on access to treatment, in future studies further use needs to be made of adjusted survival analysis, with much larger samples, and longer periods of observation, of up to at least five years. Novel therapeutic methods may need to be taken into account in the future as alternative therapies to RRT, including kidney stem cell research, xeno-transplantation and gene therapies may also need attention in the future. This is to mention only the kidney targeted therapy. Other advances are being made in the treatment of hypertension, obesity and diabetes.

9.6.3 Research on the factors that affect costs.

Further research on the factors that affect costs is needed to provide a more secure basis for modelling, with disaggregated data on transition probabilities, unit costs and opportunity costs. In terms of patient-related factors, age disease severity and co-morbidity seem likely candidates, but there may also be

factors related to treatment setting, such as teaching, district or satellite facilities – or again, public vs. private. Also there is the question of whether costs should be based on current practice or evidence-based/ high quality practice.

However this aspect needs to be addressed on a comparative European basis if Romania wants to align its renal services with the standards in the European RRT network.

Incremental cost effectiveness ratios (ICERs) and CUA (cost-utility analysis) need to become established tools in resource allocation in this medical area in Romania. This has a number of methodological implications such as the use of PPP (purchase power parity) for benchmarking purposes.

Research into the costs and levels of resource use proved difficult in this study. Data from the three centres (377 patients out of potentially about 3000 patients at the time), although from three different geographical regions, remain insufficient to draw meaningful conclusions related to treatment capacity and how efficiently this capacity was used. Better cost data are needed, and the currently available cost data need to be disaggregated.

Estimates of comparative impact are needed in terms of costs per life-year gained and QALYs, Elsewhere such methods have long since replaced resource allocation based on historic levels plus/minus increments, and they could help to address inequalities and inequities.

9.6.4 Research which may impact on quality of service and information: data sources

The two sections above outline what type of data would be needed in further research. How might these data be gathered? Good data on infrastructure are necessary for good medical practice and good quality care, as well as for good research. Given the levels of disaggregation suggested, large samples will be necessary, and with the limited numbers of cases in each treatment centre, it may be necessary to include many centres in such studies. This in turn suggests important roles for a better organised National Renal Register and a strengthened RRT register. This will require standardised definitions, with explicit inclusion and exclusion criteria and validation according to agreed and explicit rules.

Establishing a Renal Register at country level in accordance with European standards could allow the renal Romanian research network to increase its research capacity and improve the quality of research. The Romanian Register could be developed as an arm of a local Health Technology Assessment research body. The NICE kidney disease pathway could also provide a valuable tool and could be locally

adapted. Because it contains best treatment guidance for disease precursors, such as hypertension, such a pathway could provide an opportunity for prospective measurement of disease progression through stages CKD1 to CKD5.

Other sources of data, such as population surveys would have their value enhanced by cross-checking or triangulating against the renal disease register. Patient safety needs also to be taken into account, as the most sensitive and reliable CKD diagnostic through renal biopsy shows a high proportion of incidents: 9% [148]. Primary care data and National Health Insurance data could also be of help.

For good quality information to be produced, several processes need to be written into policies, including research and operational policies. Implementation will require skilled software development or purchasing, and training of staff in good governance.

9.6.5 Research to assist evidence-based decisions and policy making

According to Daniels (2000)[239] decision processes should be evidence-based, participative, transparent and accountable and the term he coined is "accountability for reasonableness". Such thinking seems to have made little headway in Romania, particularly in the healthcare system. Evidence-based decision and policy making involves bringing modellers and decision-makers together. For complete engagement, patient groups would also need to be brought in. The modelers would need to build the kinds of model that decision-makers understand and trust, and decision makers would need to accept the case for evidence-based policy making and engaging with modelers.

Much more use could also be made of approaches to priority setting such as Hanlon's P.E.A.R.L., stakeholder analyses and focus groups involving patients, and more transparent accountancy and audit systems. However it seems likely that the prospects for more rigorous decision-making will be weakened by the increasing reliance on privatised provision in the Romanian health's sector, especially under economic austerity. Certainly the decision to privatise was not evidence-based. A priori it seems likely that the 100% privatisation of the RRT network will mean self-regulated practice, which seems unlikely to improve evidence-based decision-making, at least in terms of public health, with no external audit, no quality control by independent bodies and only a weak control over physicians through the College of Physicians. This means the opposite of "accountability for reasonableness".

Primary care services are still publicly owned through the social insurance system. Primary care will continue to be the key framework for first steps and decisions to be taken in CKD management, such as

initial diagnosis of PRD, DM or HT, or referral to a nephrologist. In a cash-strapped system, primary care decision-making could go in one of two directions. For example, activity in primary care could fit in with the RRT network's vision, i.e. GPs would monitor precursor conditions and providing that primary prevention, secondary prevention with early detection, and effective treatment for DM and HT are effective, this leads to delay or avoidance of kidney damage. Effective prevention ultimately reduces the burden of CKD5 leading to RRT. In the absence of effective precursor prevention and combined with the aging of the population it may result in an increase of RRT need. The attached economic costs will lead to issues related to access to treatment, affordability, unmet need. These can be addressed once precursor conditions are addressed.

To avoid this bleak future, clinicians, researchers, policy makers and service users should establish a closer network, conduct high quality research, and implement best practice.

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Index of Appendices

APPENDIX 1

Literature Search Methodology (Medline 1966 to 2011 and list of journals)

End stage renal disease (ESRD) OR failure OR chronic kidney disease stage 5 (CKD5) AND:

RRT OR haemodialysis OR CAPD OR transplantation AND:-

definition
natural history
primary renal disease
hypertension,
diabetes
obesity
smoking
outcomes OR

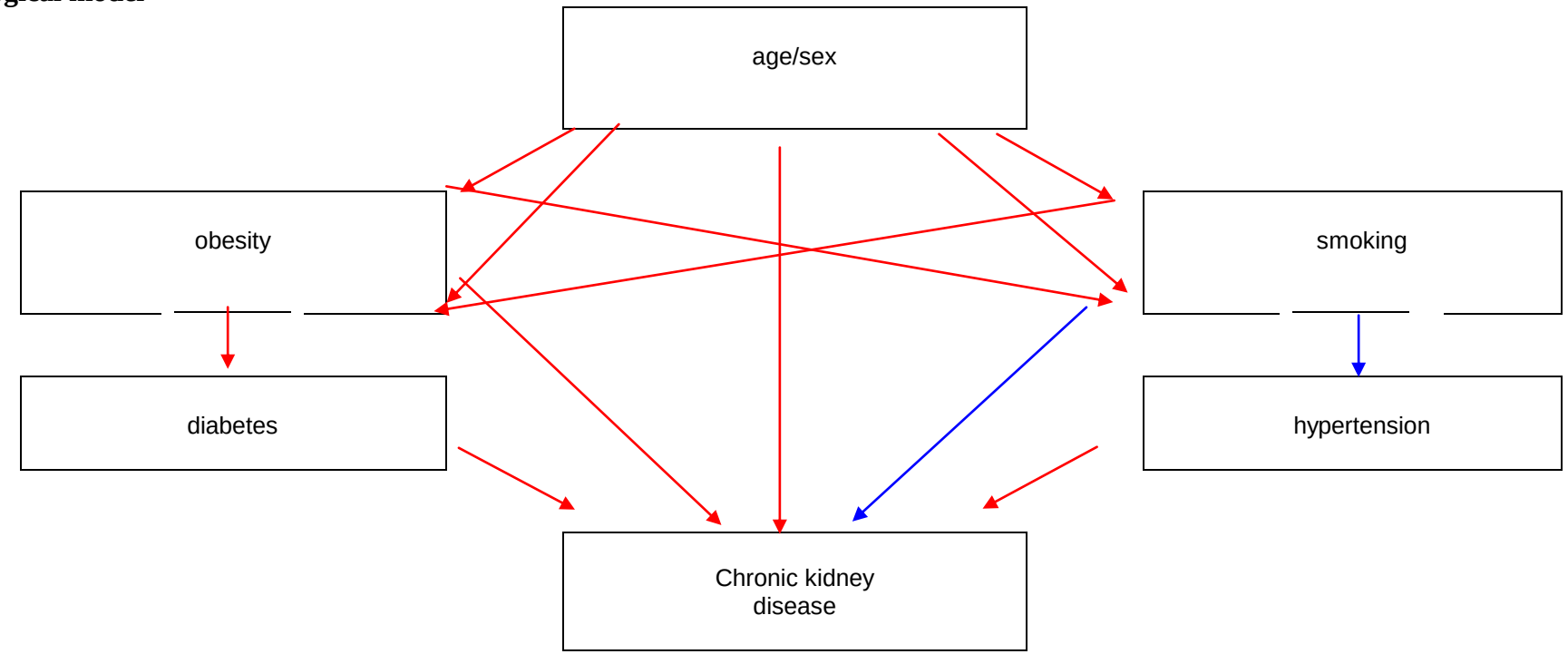
mortality
survival
quality of life OR economic value of life OR utilities
complications
co-morbidities
acceptance
stock
computer modelling OR
competitive risk analysis
decision making
costs AND
cost analyses OR CEA OR CUA
AND sample > 30

Journals from which papers were retrieved:-

1 International Journal for Technology Assessment	23. Inquiry
2 Clinical Investigations in Medicine	24. Contributions in Nephrology
3 Archives of Internal Medicine	25. American Journal in Public Health
4 British Medical Journal	26. Kidney International
5 Statistics in Medicine	27. International Journal of Artificial Organs
6 Health Care Management Review	28. Journal of American Society of Nephrology
7 American Journal of Kidney Diseases	29. Peritoneal Dialysis International
8 Journal for Health Politics, Policy and Law	30. Clinical Nephrology
9 New England Journal of Medicine	31. Scandinavian Journal of Urology and Nephrology
10 Annals of Internal Medicine	32. Advances in Peritoneal Dialysis
11 Journal of the American Medical Association	33. Journal of the Royal Society of Medicine
12 Journal of Clinical Epidemiology	34 Health Policy
13 Medical Care	35. Dialysis and Transplantation
14 Medical Decision Making	36. Health Economics
15 Journal of Chronic Diseases	37. Clinical therapy
16 Public Health Repository	38.Social Sciences in Medicine
17 Social Work in Health Care	39. Journal of Public Health Medicine
18 Nephrologie	40. American Journal of Cardiology
19. Advances in Renal Replacement Therapy	41. Nephron
20. Kidney International Supplement	42 Diabetes Care
21. Transplantation Proceedings	43. Nephrology, Dialysis and Transplantation (NDT)
22. Health Bulletin – Edinburgh	

APPENDIX 2

Epidemiological model



Legend to figure

Smoking and hypertension	No independent relationship	Primatesta et al Hypertension 2001; 37: 187-193 John U et al QJ Med 2006; 99: 407-415		
Obesity and hypertension	Independent relationship	John U et al QJ Med 2006; 99: 407-415	BMI < 25	BMI 30+

			BMI < 25	BMI 30+
		Mokdad A et al JAMA 289: 76-79	BMI < 25	BMI 30-39
Smoking and diabetes	Independent relationship	Willi C et al JAMA 2007; 298: 2654-2664	smokers	non-smokers
Obesity and diabetes	Independent relationship	Colditz et al Ann Int Med 1995; 122: 481-86		
		Mokdad A et al JAMA 289: 76-79	BMI < 25	BMI 30-39
		Wannamethee G et al J Ep Comm Hlth 2005: 59:134-39	BMI < 25	BMI 27.5-29.9
				BMI 30+
Smoking and PRD	No independent relationship (?)	Fox C et al JAMA 2004; 291: 844-50	smokers	non-smokers
Obesity and PRD	No independent relationship	Fox C et al JAMA 2004; 291: 844-50	per unit BMI	
	Independent relationship	Hsu C et al. Ann Int Med 2006; 144:21-23	BMI < 25	BMI 30-39
Hypertension & CRD	Independent relationship	Fox C et al JAMA 2004; 291: 844-50	140/90 or on medication	
Diabetes & CRD	Independent relationship	Fox C et al JAMA 2004; 291: 844-50	140/90 or on medication	
	non-obese	Hsu C et al. Ann Int Med 2006; 144:21-23	BMI < 25	BMI 30-39
	Obese			

APPENDIX 3

1997 EDTA RRT data: Accepted and Stock of patients - Romania

NEW **patients**				**aged <15**				**DEATHS**				**DEATHS aged <15**				**STOCK - Location**			
HD	PD	Tx	Total	HD	PD	Tx	Total	HD	PD	Tx	Total	HD	PD	Tx	Total	Centre HD	Self limited care HD	Home HD	Total
514	48	16	578	34	1	3	38	173	6	2	181	9	0	0	9	1355	0	0	1355
34 centres recorded on database 25 responded as at 3 1/12/97 This data therefore represents 74% of centres in Rumania																			

STOCK - Type of treatment				**STOCK - Location - aged <15**				**STOCK - Type of treatment - <15**				**Alive & treated by PD**			
HD	Haemo-filtration	Haemo-diafiltration	Total	Centre HD	Self limited care HD	Home HD	Total	Total	HD	Haemo-filtration	Haemo-diafiltration	CAPD	Auto PD	Other PD	Total
1349	0	6	1355	44	0	0	44	44	0	0	44	128	1	0	129

Alive & treated by PD - aged <15				**Alive_with_functioning_graft**				**Alive with functioning graft - <15**				**HD to Tx**		**PD to Tx**	
CAPD	Auto PD	Other PD	Total	your centre	another centre	another country	Total	your centre	another centre	another country	Total	Total	<15	Total	<15
1	0	0	1	67	94	14	175	5	4	0	9	59	5	5	0

1997 EDTA data: Stock of patients - Romania continued

Tx to HD		Tx to PD		PD to lID		HD to PD		Total renal_grafts			Total 1st_grafts			Total 1st grafts aged <15		
Total	<15	Total	<15	Total	<15	Total	<15	Cadaver	Living	Total	Cadaver	Living	Total	Cadaver	Living	Total
22	0	0	0	6	1	17	1	7	31	38	6	31	37	0	2	2

All Regrafts			All_Regrafts_aged_<15			Multiple grafts				Tx			Total Tx - <15		
Cadaver	Living	Total	Cadaver	Living	Total	kidney/ pancreas	kidney /liver	kidney/ heart	Total	Cadaver	Living	Total	Cadaver	Living	Total
1	0	1	0	0	0	0	0	0	0	7	31	38	0	2	2

Total Tx – 15 to 59			Total Tx - ≥60			Total grafts			Total grafts - 1st graft			Total grafts - regraft		
Cadaver	Living	Total	Cadaver	Living	Total	Cadaver	Living	Total	Cadaver	Living	Total	Cadaver	Living	Total
7	29	36	0	0	0	9	88	97	8	88	96	1	0	1

Source: ERA-EDTA Registry, St Thomas' Hospital London, England

Summary table of respondent and non-respondent centres: EDTA and CQ (CQ form in APPENDIX 4)

Centre	*No of pts*	Centre	No. of pts	*Centre*	*No. of pts*	*Centre*	*No. of pts.*
***1** Centre BH*	*116*	**9** Centre AB	47	17 respondent EDTA Buch CD	-	25 respondent EDTA MH	-
***2** Centre BV*	*112*	**10** Centre BN	36	18 respondent EDTA Buch U	-	26 respondent EDTA PH	-
***3** Centre HD*	*27*	**11** Centre CV	23	19 respondent EDTA TM	-	27 respondent EDTA SB	-
***4** Centre Bucharest F*	*82*	**12** Centre SJ	33	20 respondent EDTA CJ1	-	28 respondent EDTA SV	-
***5** Centre CT*	*83*	**13** Centre Bucharest SFI	175	21 respondent EDTA CJ2	-	29 respondent EDTA VL**	-
***6** Centre DJ*	*104*	**14** Centre Bucharest NP	112	22 respondent EDTA MS	-	30 non-respondent EDTA or CQ	-
***7** Centre IS**	*186*	15 unusable patient data	CQ	23 respondent EDTA AR	-	*EDTA adult (1 to 7; 17 to 30)*	*1605*
8 Centre OT	*26*	16 unusable patient data	CQ	24 respondent EDTA CS	-	*CQ 1 to 14 (adult ≥ 15 years)*	*1162 (1150)*

**Centres 1 to 7 reported to both EDTA and CQ for the 1997 cohort totalling n =710 patients; 94 were excluded due to:-*

a) age <15 (n=48)

b) incomplete data n=46 (e.g. centre IS reported 186 patients; however, only 146 HD patients had data eligible for analysis; centre BV reported 112 and 106 were eligible, centre Bucharest SFI reported 175 and 148 were eligible) and

c) CAPD and Tx patients were difficult to cross-check for registration with a specific centres and national estimates were used in the treatment model. The 7 centre, which reported to both EDTA and CQ, had an estimated pool of 616 to 662 patients and the lowest value and closest to the validated estimate was chosen for the CRM (Chapter 6, Section 6.5 and Chapter 10). Cross-check validation of reported numbers with actually collected figures was only possible for the 3 sampled centres: Bucharest, Iasi and Brasov

***some other 13 centres reported figures to the EDTA. These were not available to this study, neither in aggregate numbers, nor in detail. The difference of 1605 – 616 = 989 adult patients was used in the CRM*

**** For the CQ data source the difference of 1150- 616 =534 was used in the CRM (Chapter 6, Section 6.5, Table 6.2).*

APPENDIX 4

Centre Questionnaire (CQ)

ROMANIA

Centre (code): ☐☐☐☐

1. year in which the centre was set up ☐☐☐☐

2. number of patients treated (1995, 1996, **1997** - **stock**/year) ☐☐☐ 1995

☐☐☐ 1996

☐☐☐ **1997**

3. number of new patients (1995, 1996, **1997**- acceptance) ☐☐☐ 1995

☐☐☐ 1996

☐☐☐ **1997**

4. distribution of patients according to the modality of RRT treatment

1995: ☐☐☐ ☐☐☐ ☐☐☐

HD/HDF CAPD LRTx

1996: ☐☐☐ ☐☐☐ ☐☐☐

HD/HDF CAPD LRTx

1997: ☐☐☐ ☐☐☐ ☐☐☐

HD/HDF **CAPD** **LRTx**

5. On HD: total number of stations ☐☐

total number of **(functional)** dialysis stations ☐☐

type(s) of machine

(firm):_____-

-_____-_____

year of purchase: ☐☐☐☐

types of membranes used (tick): ☐ cellulosic ☐ non-cellulosic fill in: ☐☐ mixed (%) ☐☐

dialysate type (tick): ☐ acetate ☐ bicarbonate

6. On CAPD: type of system connection: ☐☐ single bag ☐☐ twin bag ☐☐ other

7. dedicated human resources:

a. physicians ☐☐

b. nurses ☐☐

c. ancillary ☐☐

d. other (no.) ☐☐

e. other (shared) profile*: ☐☐ physicians ☐☐ nurses ☐☐ ancillary ☐☐ other

a_____-_____

b_____-_____

c_____-_____

d_____-_____

e _____-_____

8. RRT financial resources (1997 **budget)** ☐☐☐☐☐☐☐☐☐ Lei

[US$ ☐☐☐☐☐]

9. catchment area for the centre (population)

10. total health budget of the main district health authority (1997)

Lei

[US$]

APPENDIX 5

Letter for Centres (CQ and Patient Form data collection)

APPENDIX 6

PATIENT FORM- BASELINE and FOLLOW-UP

BASELINE

PART A ***Centre Code****

I. Sociodemographic data:

1. ID

(**d d m m y y** S p F D D)

2. [age at first RRT (yrs)]

3. gender (M, F)

4. first referred to a nephrologist (dd/mm/yy)

5. type of referral (self, GP, other)

6. **treatment started (date of first entrance)(dd/mm/yy)** **9 5**

7. socioeconomic status:

   - education (school)
   - occupation at entry on RRT
   - marital status
   - residency
   - distance to RRT centre (km)
   - means of transport

II. Medical data

1. primary renal disease (PRD)

2. co-morbidity (underlying morbidity by the time RRT scheme started)

Group [code]

3. medication (chronic) at start

of RRT (tick): CV HAEM INF ENDO NEUR-PSIH BONE DIG PULM OTHER

4. type of first RRT

5. stage of chronic renal insufficiency when RRT started

- serum creatinine (mg/dL)
- Ht (%)
- Hb (g/dL)
- serum albumin (%)
- X-ray (plain renal) (yes/no) if yes, size of kidneys (cm) L

R

6. BP (mmHg)
7. Weight (kg)
8. Height (cm)

III RRT:

HD

9. Type of vascular access:

Cimino-Brescia ☐ Scribner shunt ☐ Shaldon catheter ☐ other ☐

date performed ☐☐☐☐☐☐ attempts ☐ funct (ml/min) ☐☐☐
(if Cimino-Brescia)

surgical complications ☐

CAPD

10. Type of access:

single bag ☐ twin bag ☐ other ☐ date performed ☐☐☐☐☐

first access complications ☐ type: ☐

Tx

10. Living related:

date performed: ☐☐☐☐☐☐

postoperative complications ☐

1-YEAR FOLLOW-UP (cohorts ’95, ’96 and ’97)

PART B ***Centre code **** ☐☐☐☐

II. Medical data **31 Dec 95-96-97**

ID ☐☐☐☐☐☐☐☐

(d d m m y y S p F D D)

occupation (employment status) ☐

1. other co-morbidity detected in the first year of treatment ☐

medication (chronic)-(tick) ☐

☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

CV HAEM INF ENDO NEUR-Psych BONE DIG PULM OTHER

type of RRT ☐

2. actual registration with GP (yes/no) ☐

3. disease status and biological results at 1 year* ☐

- total number of HD sessions ☐

- duration of session (average) hours ☐ min ☐

- serum creatinine (mg/dL) ☐

- Ht (%) ☐

- Hb (g/dL) ☐

- serum albumin (%) ☐

4. BP (mmHg) ☐☐

5. Weight (kg) ☐

**** for these variables: to consider either last measurement (i.e. if done quarterly) or average of last three measurements if done monthly)***

Treatment interruption

short interruption

reason

from

from

from to

transfer

date type of treatment **reason**

date type of treatment reason

lost to follow-up

date

death

date **cause**

2-YEAR FOLLOW-UP (cohorts ’95 and ’96)

Centre code *

II. Medical data **31 Dec 96-97**

ID (d d m m y y S p F D D)

occupation (employment status)

1. other co-morbidity detected in the first year of treatment

2. medication (chronic)-(tick)

CV HAEM INF ENDO NEUR-PSIH BONE DIG PULM OTHER

3. type of RRT

4. actual registration with GP (yes/no)

5. disease status and biological results at 2 year*

- total number of HD sessions
- duration of session (average) hours min
- serum creatinine (mg/dL)
- Ht (%)
- Hb (g/dL)
- serum albumin (%)

6. BP (mmHg)

7. Weight (kg)

**** * for these variables: to consider either last measurement (i.e. if done quarterly) or average of last three measurements if done monthly)***

VII. Treatment interruption

short interruption

reason

from

from

from to

transfer

date type of treatment **reason**

lost to follow-up

date

death

date **cause**

3- YEAR FOLLOW-UP (cohort '95)

Centre code *

II. Medical data **31 Dec '97**

ID

(d d m m y y S p F D D)

occupation (employment status)

8. other co-morbidity detected in the first year of treatment

9. medication (chronic)-(tick)

CV HAEM INF ENDO NEUR-psych BONE DIG PULM OTHER

10. type of RRT

11. actual registration with GP (yes/no)

12. disease status and biological results at 2 year*

- total number of HD sessions

- duration of session (average) hours min

- serum creatinine (mg/dL)

- Ht (%)

- Hb (g/dL)

- serum albumin (%)

13. BP (mmHg)

14. Weight (kg)

**** * for these variables: to consider either last measurement (i.e. if done quarterly) or average of last three measurements if done monthly)***

VII. Treatment interruption

short interruption

reason

from

from

from to

transfer

date type of treatment **reason**

lost to follow-up

date

death

date **cause**

APPENDIX 7

Clinical outcomes: descriptive analysis in sampled units

Variable	Centre 1 (T)			Centre 2 (T)			Centre 3 (D)			Total		
	1995	1996	1997	1995	1996	1997	1995	1996	1997	1995	1996	1997
Socio-demographic												
HD	61	56	43	53	49	38	23	27	34	**147**	**132**	**115**
CAPD		10	11	4	16	14	-	-	-	**4**	**26**	**25**
Exclusions												
< 90 days												
deaths[a]	10	5(1)	-	2	1	2(1)	-	-	1	12	6(1)	3(1)
lost f-up	5	3(2)	8	3	-	-	-	-	-	8	3(2)	8
recovery	-	-	-	-	-	1	-	-	-	-	-	1
> 90 days	4	6(1)	1	4(1)	(4)	3(3)	-	-	-	8(1)	6(5)	4(3)
N= 377	42	48	45	57	60	42	23	27	33	122	135	120
HD= 335	42	42	34	54	48	32	23	27	33	**119**	**117**	**99**
CAPD= 42	0	6	11	3	12	10	-	-	-	**3**	**18**	**21**
Sex M:F	24:18	35:13	30:15	32:25	35:25	22:20	13:10	16:11	21:12	69:53	86:49	73:47
ratio	1.3	2.7	2.0	1.3	1.4	1.1	1.3	1.5	1.8	1.3	1.8	1.5
Age												
Average ± sd	42.9 ±14.41	47.5± 11.85	45.7±12.3	42.4±10.9	40.8±13.0	42.7±13.5	49.4±13.4	50.0±13.5	43.8±13.5	43.9±13.7	45.0±12.3	44.1±13.0
HD	42.9± 14.41	46.3±11.9	46.4±12.8	42.2±11.4	41.1±13.2	42.8±13.7	49.4±13.4	50.0±13.5	43.8±13.5	43.8±13.8	45.0±12.5	44.4± 13.3
CAPD	N/A	56.5±6.3	43.5±10.8	46.6±10.8	39.8±8.8	42.2±14.3	N/A	N/A	N/A	46.6±10.8	45.3±11.3	42.9±11.9
Median	44	46	49				52	52	44	45	45	44
≥ 60	4	11	9	4	2	5	7	7	4	15	20	18
HD	4	8	8	4	2	4	7	7	4	15	17	16
CAPD	N/A	3	1	0	0	1	N/A	N/A	N/A	0 (12%)	3 (15%)	2 (15%)
Age group distribution											%		%		%
< 25	6	1	3(1)	4	4(1)	3	1	1	3	11	9	6(1)	5	9(1)	8
25 – 44	17	18	14(5)	24(2)	24(7)	14(6)	6	9	14	47(2)	40	51(7)	43	42(11)	44
45 – 64	17	21(6)	14(5)	25(1)	19(4)	13(4)	14	14	15	56(1)	47	54(10)	47	42(9)	43
≥ 65	2	2	3	1	1	2	2	3	1	5	4	6	5	6	5

[a] CAPD patients in brackets

Clinical outcomes: descriptive analysis in sampled units (continued)

Variable	Centre 1 (T)			Centre 2 (T)			Centre 3 (D)			Total		
	1995	1996	1997	1995	1996	1997	1995	1996	1997	1995	1996	1997
Underlying cause of ESRF												
PRD	31	33(5)	33(9)	44(3)	41(9)	23(5)	13	15	20	88(3)	89(14)	76(14)
HT	2	1	(2)	1	0	2	5	6	4	8	7	6(2)
DM	0	0	0	2	2(2)	3(2)	2	1	0	4	3(2)	3(2)
Systemic	1	0	0	1	3(1)	0	2	4	0	4	7(1)	0
Unknown	8	8(1)	1	6	2	4(3)	1	1	9	15	11(1)	15(2)
Co-morbidity @ baseline												
- at least one	17	8(5)	30(7)	21(1)	34(11)	14(7)	20	24	29	58(1)	66(16)	73(14)
- one	6	7(2)	12(1)	20(1)	16(7)	9(2)	20	24	21	47(1)	47(9)	42(3)
- two	11	1(2)	14(3)	1	17(3)	4(4)	0	0	8	11	18(5)	26(7)
- three	0	0(1)	4(3)	0	1(1)	1(1)	0	0	0	0	1(2)	5(4)
- none	25	35	4(4)	33(2)	14(1)	18(3)	3	3	4	61(2)	52(1)	26(7)
- HT	13	3(1)	13(6)	16(1)	23(10)	5(5)	7	10	10	36(1)	36(11)	28(11)
Cardio-vascular												
- one	16	6(4)	16(7)	16(1)	25(10)	8(6)	13	12	12	46	57	49
- > one	7	0(1)	6(3)	0	3(1)	1	0	0	0	7	5	10
Diabetes (NIDDM and IDDM)	0	0	2(1)	2	2(2)	4(2)	2	1	0	4	3(2)	3(2)
Haematology (Anaemia)	0	0(2)	16(3)	2	6	4(2)	5	9	23	7	15(2)	48(5)
Cancer	1	0	1(1)	0	1	1	0	0	0	1	1	2(1)
All other [b]	6	5(2)	5(1)	2	10(3)	3(1)	2	0	3	10	15(5)	11(2)

[b] surgical removal of gall bladder, obesity, lithyasis, Sharp syndrome, testicular ectopia, UTI, umbilical hernia, TB, corneal ulcer, benign hypertrophy of prostate, nephrectomy, appendicitis, duodenal ulcer, liver cyst, poliserositis, fracture of spine, hypofisa adenoma, rheumatoid arthritis

Clinical outcomes: descriptive analysis in sampled units (continued)

Variable	Centre 1 (T)			Centre 2 (T)			Centre 3 (D)			Total		
	1995	1996	1997	1995	1996	1997	1995	1996	1997	1995	1996	1997
Deaths in first year	13	7(2)	8(1)	7	6	8(1)	0	3	4	20	16(2)	20(2)
(%) Overall first year mortality rate	31	19	20	12	10	21	0	11	12	16	13	18
- HD	31	17	24	13	13	25	0	11	12	16	14	20
- CAPD	N/A	33	9	0	0	10	N/A	N/A	N/A	0	11	10
TREATMENT												
	Type of vascular access at start of RRT (HD only)											
Catheter	32	32	28	35	32	23	0	0	1	67	54	52
Shunt	3	3	0	0	0	1	0	0	0	3	3	1
a-v fistula	7	17	6	11	11	6	23	27	32	40	55	44
Not specified	-	-	-	9	5	2	-	-	-	9	5	2
Type of membrane [b]												
Cellulose m.	100			75		25	75		75	75	23	41
Synthetic m.			100	25		75	25		25	25	77	59
Dialysate buffer												
Acetate						50			100			District mostly
Bicarbonate			100			50						Teaching mostly

[b] Figures from 1995 and 1996 are taken from the National Registry; 1997 figures were collected via Centre Questionnaire

APPENDIX 8

Accounting Costs

Chapter 6

Table 0.1: HD cost/ patient, Romania, 1997 (US$)

Consumables and drugs			
Item	*Unit*	*Quantity*	*USD*
Artificial kidney (membrane)	Item	1	16.61
Blood lines (set)	Item	1	4.10
Needles (fistula)	Item	2	0.98
Dialysis set (TOTAL)			21.69*
Concentrate solution : Acid Basic	 litre litre	 5 7	18.93
Drip line	Item	2	0.50
Syringe 30 ml	Item	1	0.62
Syringe 2 ml	Item	4	-
Syringe 5 ml	Item	2	-
Syringe 10 ml	Item	2	-
Gloves (single use)	Pair	2	0.62
Drugs			5.31
EPO	I.U.	Varies	1.07
Dressings and other materials	-	-	1.12
Blood	ml PRBC**		1.16
Disinfectant Puristeril	 Ml		 0.19
SUB-TOTAL (I) direct cost			51.31

Table 0.2 continued

Other expenditure (cost)/patient	*USD*
Hospitalisation (average/year)	10.84
Tests	3.82
Food	0.58
Water	0.02
Equipment –depreciation	2.83
Water station depreciation	0.61
Equipment –spares	0.22
Patient's transport	6.57
Rest Room	0.25
Laundry	0.25
Electricity	0.42
Heating	0.14
Cleaning (materials)	4.84
Salaries	4.84

SUB-TOTAL (II)	44.50

TOTAL (I + II) HD session	95.81

*salaries, according with firm they are bought from: 21.00 to 25 USD; **PRBC –packed red blood cells

Table 0.2: CAPD cost/ patient, Romania, 1997 (USD)

Consumables	*Quantity*	*USD*
Tenchkoff catheter	1	56.50
Catheter extension	2	17.32
Catheter adapter	2	4.24
CAPD double bags	1,500	8,625
Clamps	1,500	840
"Frekaderm"	52	338
SUB-TOTAL I		9,881.06

Table 0.3: CAPD cost/ patient, Romania, 1997 (US$) - continued

Other expenses/ patient		
	Unit	*USD*
Hospitalisation	28 days/y	5,725.25
Drugs (while hospitalised)		366.31
Periodical tests		623.33
SUB-TOTAL II		6,714.89

TOTAL I + II CAPD	16,595.95

Table 0.4: *Monthly Tx maintenance cost/ patient, Romania, 1997 (US$)*

Item	*USD*
Medical check-up	1.8
Tests	7.2
Hospitalisation	36.4
Drugs	
- Cyclosporine (200 tb/month)	547.50
- Azathioprine (100 tb/month)	36.00
- Steroids ("Prednison") (300 tb/month)	13.50
TOTAL cost/month	632.40
TOTAL cost / year	7,588.80

APPENDIX 9 Cost Form

Costing

1. Unit of output: HD session (then a.e.c.), CAPD session 1 and monthly (then AC)
   'Tx pre-, Tx, post- episodes of care (a.e.c.)
2. Resources to be identified (Ingredients list; sublists by modality)
3. Values to be attached; find marginal costs and perform the survival analysis
4. Model building
5. Sensitivity analysis

Itemised list RRT

1 **STAFF**

doctors
- nephrology
- urology
- ICU
- vascular surgery
- internal medicine
- haematology
- Radiology
- other specialty

psychologist

dietitian

nurses
- Centre
- Ward
- Theatre
- Other

ancillary /catering
- Centre
- Rx
- Lab
- Ward
- Kitchen
- Other

pharmacy
- Chemist
- Assistant

lab
- Biologists
- Chemistry

technical comp
- Engineers
- technicians

TC staff **Opp staff**

2 **AMBULANCES**
- Driver
- Petrol
- Maintenance
- Deprec

TC ambulance **Opp. driver**
(cost/journey)

3 **BUILDINGS**
- deprec
- maintenance
- rent
- electricity
- dialysis ward
- phone line
- heating

T. overhead **Opp. building**

4 **ADMIN**
- accountants
- mgt
- receptionists
- personnel

Overhead admin **Opp admin**

5 **DIALYSIS EQUIPMENT (HD)**
- machine
- PTFE graft
- shunt
- catheter
- Shaldon
- Other

dialyser [see list]

6 **CAPD EQUIPMENT**
- Y-bag
- other
- disinfectant
- clamps
- dressings

TC equipment

aa line
vv line
aa access
vv access
uni-access
shunt connector
aa loop
vv loop
Single use needles
Single use gloves
syringe 2ml
5 ml
10 ml
30 ml
other syringe
disinfectant
dressings
water purif.

TC HD equipm

7 **DRUGS (I)**

fluids
saline .9%
saline 10%
saline 20%
glucose 20%
dialysate 1(conc)
dialysate 2(conc)
KCl 7.4%

other (drugs)
heparine
protamine sulphate
vit K
Ca gluc 10%
cardiac
antibiotics
vascular (BP)
blood
EPO
alfa-calcidiol
steroids
sedatives
insuline
antialgics

TC drugs (I)

other (fluids)
WATER

8 **ROUTINE INVESTIGATIONS**

Hb
Ht
Ret
L
Tr
BT
CT
PTT, Howell
Urea(s)
Creat(s)
Uric ac.
Na^+
K^+
Ca^{2+}
PO_4^{3-}
HCO_3^-
Fe
Transf
Acid phosph..
Alk. phosph

9 **SPECIAL INVESTIGATIONS**

fibroscopy
haemocult
HLA Ag
other special

TC special

10 **PATIENT**

drugs
transport

TC patient
(transfer costs)

		ALAT
		ASAT
		Ag HBs
		Ab VHC
		HIV
		Billirubin
		Electrophoresis
		Glycaemia
		Lipids
	Rx	Plain X-ray kidney
		Chest X-ray
		Bones X-ray
		Films
		Solutions
	Other	ECG
		Oscillometry
		Eye test
		EMG
		EEG
		Neurological
		ENT
		TC Routine
11	**HOSPITAL DRUGS (II)**	
	antibiotics	
		Ampicyllin
		Ceftriaxon
		Vancomycin
		Amoxicillin
		Cefuroxim
		Cetirizin
		Nicetamide
		Neomycin
	cardiac	Deslanosid
		Dopamine
		epinefrine
		etilefrine
		frusemide
		lydocain
		nitroglycerin
		nipride
		propafenone
	vascular (BP)	
		aminophyllin
		carbazocrom
		DH-ergotoxin
		etamsilat
		papaverine

11	**HOSPITAL DRUGS (II) cont'd**	
	beta blockers 1	
		propranolol
	beta blockers 2	
		metoprolol
		astemisol
	others	
		captopril
		clonidin
	Ca blockers	
		nifedipin
		verapamil
	Blood	
		carbocromen
		ticlopidine
		thrombine
	sedatives	
		clemastin
		clopromazine
		diazepam
		phenobarbital
	steroids	hydrocortisone hemisuccinate

	other **insuline** humulin others **Pain medication** algocalmin piafen **TC DRUGS (II)**

List of dialysers ***(Source: http//:www.hdcn.com)*** **tick one or more**

Althin
Asahi
Baxter
Cobe
Fresenius
Gambro
Gambro/HOS
Minntech
N.M.C.
Organon
Terumo
Toray

Membrane

Cellulosic	
non-cellulosic	

Dialysate (tick)

Acetate	
bicarbonate	

APPENDIX 10

NATIONAL KEY PERSONS INTERVIEWS

Interview questions - key persons at national level

- Q1. Awareness of resource allocation for RRT in the health service
    - How does the Programme receive its budget?
- Q2. Awareness on proportions spent: within programmes, among programmes, among other medical specialities which 'compete' with nephrology:
    - what are the resource distribution policies?
    -is geographical equity a consideration?
- Q3. WHAT are the competitive specialities?
    -enumerate
- Q4. How will be the PROVISION of RRT be affected in the context of changes in the health service (from tax based to public insurance)?
- Q5. Awareness of the application of national treatment and access protocols:
    -who makes them
    -what do they consist of (i.e. including transplantation legislation, etc.)?
    -do the protocols include policies about prioritisation between groups of patients where service provision is insufficient (e.g. age, PRD, etc.?)
    - what are the policies and instruments relating to adherence to protocols at the local level?
- Q6. Awareness of application of any other local protocols (i.e. at district level: who makes them? are they applied along with the national protocols? are they applied instead of the national protocols?
- Q7. Plausible policy scenarios to be examined at the modelling stage:
    - is the extension of the use of satellite units (teaching, district) plausible as part of a future service configuration?
    -if none of these are considered for service extension, what are the constraints (money, human resources, etc.?)

LOCAL KEY PERSONS INTERVIEWS

Interview questions -key persons at local level (Cohort of 1997)

Treatment and access protocols:

- Q1. adherence to national treatment protocol (dialysis committee); if not, why?
- Q2. local protocol concerning treatment:
  - access,
  - duration of typical HD session, and
  - number of sessions per week on individual patients (range and durations).
- Q3. catchment area:
  - individual patient's distance from centre
  - means of transport for each patient
- Q4. adherence to the EDTA/ERA, if yes:
  - year
  - 1997 data

Budget and expenses

- Q5. financial flow and costs of the unit: fiscal year of 1997
- Q6. provide 'itemised' list
- Q7. provide subsequently the sub-lists by modality of treatment, in order to be valued
- Q8. overheads
  - HOW are they measured, and
  - WHAT are their components?
- Q9. hospitalization costs: clinical notes and values attached to hospitalization ingredients
- Q 10. any identifiable priority areas for renal replacement therapy in Romania? (open question)

 # Q1-5 and partially Q9 (on clinical notes): Centre's Clinical Director; #Q5-9: Centre's accountant and hospital's accountant, #Q10 : all levels of management: clinical director, pharmacy and supplies, nurse manager, accountant, other.

APPENDIX 11 **The treatment model (spreadsheet)**

1,150	CQ 1997	(53%)	
1,659	EDTA Q 1997	(74%)	incl. paediatric units
1,605	EDTA Q 1997	(70%)	excl. paediatric units
		(resulting in both sources covering 71% of all national stock)	
2,995	NUE from CRM		*95% CI from2,869 to 3,121*
3,170	(Ref 16)	(100%)	

BASELINE

a mortality 13% on HD, 5% on CAPD and 4% on Tx

CRM **Chapter 4 (Section 4.3.2) and Chapter 7**

=from $x12 to $x31

	A	B	c	a+b	a+c	a+b+1	a+c+1	a+1	mle =($e12*$f12)/$b12	nue =[($g12*$h12)/$i12]	=$k12-1
1997	616	989	534	1605	1150	1606	1151	617	2996	2996	**2995**
1998	748	1205	646	1944	1404	1945	1405	749	3647	3646	**3645**
1999	865	1389	749	2241	1628	2242	1629	866	4216	4216	**4215**
2000	968	1551	840	2501	1826	2502	1827	969	4717	4716	**4715**
2001	1059	1691	921	2728	2002	2729	2003	1060	5158	5157	**5156**
2002	1139	1815	992	2928	2157	2929	2158	1140	5546	5546	**5545**
2003	1209	1924	1056	3103	2295	3104	2296	1210	5889	5889	**5888**
2004	1272	2019	1112	3257	2418	3258	2419	1273	6193	6192	**6191**
2005	1327	2104	1162	3393	2527	3394	2528	1328	6461	6461	**6460**
2006	1376	2178	1207	3513	2624	3514	2625	1377	6699	6699	**6698**
2007	1420	2244	1247	3619	2711	3620	2712	1421	6911	6911	**6910**
2008	1458	2301	1282	3712	2788	3713	2789	1459	7098	7098	**7097**
2009	1493	2353	1315	3795	2858	3796	2859	1494	7266	7266	**7265**
2010	1524	2399	1343	3869	2920	3870	2921	1525	7415	7415	**7414**
2011	1551	2440	1369	3935	2976	3936	2977	1552	7550	7549	**7548**
2012	1576	2476	1392	3993	3026	3994	3027	1577	7668	7668	**7667**
2013	1598	2509	1413	4046	3071	4047	3072	1599	7776	7776	**7775**
2014	1618	2537	1432	4092	3112	4093	3113	1619	7872	7871	**7870**
2015	1636	2563	1449	4134	3149	4135	3150	1637	7959	7958	**7957**
2016	1652	2587	1464	4172	3183	4173	3184	1653	8038	8038	**8037**

Scenario Baseline a (continued)

=(a+b+1)(a+c+1)(b)(c)/(a+1)2 (a+2)

var NUE

					95% CI	
=($g12*$h12*$c12*$d12)	=$i12*$i12	=($b12+2)*$n12	=$m12/$o12	=SQRT($p12)	=$L12-1.96*$q12	=$L12+1.96*$q12
9.76244E+11	380689	235265802	4150	64	**2869**	**3121**
2.1272E+12	561660.314	421492365.7	5047	71	**3574**	**3785**
3.80017E+12	750562.323	651000230.4	5837	76	**4138**	**4364**
5.95374E+12	939368.024	911384250.7	6533	81	**4635**	**4874**
8.51417E+12	1123303.22	1191667454	7145	85	**5072**	**5322**
1.13852E+13	1298938.88	1481712574	7684	88	**5457**	**5717**
1.44746E+13	1464632.45	1773992114	8159	90	**5798**	**6065**
1.77015E+13	1619739.84	2063046432	8580	93	**6099**	**6373**
2.09811E+13	1763477.76	2343591406	8953	95	**6365**	**6646**
2.42506E+13	1895991.3	2612581215	9282	96	**6602**	**6887**
2.74705E+13	2018047.54	2868816017	9576	98	**6812**	**7102**
3.0565E+13	2128797.72	3108129825	9834	99	**6997**	**7291**
3.3571E+13	2231169.56	3334951459	10066	100	**7164**	**7461**
3.64228E+13	2324130.74	3545484685	10273	101	**7313**	**7613**
3.91346E+13	2409231.71	3741946413	10458	102	**7446**	**7749**
4.16618E+13	2485951.36	3922060595	10622	103	**7564**	**7869**
4.40565E+13	2556513.19	4090191015	10771	104	**7671**	**7978**
4.62749E+13	2620254.44	4244078519	10903	104	**7766**	**8075**
4.83592E+13	2678754.16	4386968894	11023	105	**7852**	**8163**
5.03213E+13	2732706.55	4520142574	11133	106	**7931**	**8243**

Baseline continued

b mortality 50% increase

									mle	**nue**	
	A	B	c	a+b	a+c	a+b+1	a+c+1	a+1	=($e12*$f12)/$b12	=[($g12*$h12)/$i12]	=$k12-1
1997	616	989	534	1605	1150	1606	1151	617	2996	2996	**2995**
1998	748	1149	615	1853	1338	1854	1339	749	3313	3312	**3311**
1999	865	1273	687	2054	1493	2055	1494	866	3544	3544	**3543**
2000	968	1375	747	2217	1623	2218	1624	969	3716	3716	**3715**
2001	1059	1457	796	2350	1731	2351	1732	1060	3842	3842	**3841**
2002	1139	1525	838	2459	1821	2460	1822	1140	3932	3933	**3932**
2003	1209	1580	873	2548	1897	2549	1898	1210	3997	3998	**3997**
2004	1272	1626	902	2622	1961	2623	1962	1273	4043	4044	**4043**
2005	1327	1663	927	2683	2015	2684	2016	1328	4074	4075	**4074**
2006	1376	1695	949	2734	2062	2735	2063	1377	4097	4098	**4097**
2007	1420	1721	966	2776	2101	2777	2102	1421	4109	4109	**4108**
2008	1458	1743	982	2812	2135	2813	2136	1459	4118	4118	**4117**
2009	1493	1763	996	2843	2165	2844	2166	1494	4123	4124	**4123**
2010	1524	1779	1007	2869	2190	2870	2191	1525	4124	4125	**4124**
2011	1551	1792	1018	2891	2213	2892	2214	1552	4124	4125	**4124**
2012	1576	1805	1027	2911	2232	2912	2233	1577	4123	4124	**4123**
2013	1598	1815	1035	2927	2249	2928	2250	1599	4120	4120	**4119**
2014	1618	1824	1042	2942	2265	2943	2266	1619	4119	4120	**4119**
2015	1636	1832	1048	2955	2278	2956	2279	1637	4115	4116	**4115**
2016	1652	1839	1053	2966	2290	2967	2291	1653	4111	4112	**4111**

=(a+b+1)(a+c+1)(b)(c)/(a+1)2 (a+2)

var NUE

					95% CI	
=($g12*$h12*$c12*$d12)	=$i12*$i12	=($b12+2)*$n12	=$m12/$o12	=SQRT($p12)	=$L12-1.96*$q12	=$L12+1.96*$q12
9.76244E+11	380689	235265802	4150	64	**2869**	**3121**
1.75538E+12	561660.314	421492365.7	4165	65	**3247**	**3438**
2.68517E+12	750562.323	651000230.4	4125	64	**3479**	**3669**
3.69642E+12	939368.024	911384250.7	4056	64	**3652**	**3840**
4.72406E+12	1123303.22	1191667454	3964	63	**3778**	**3964**
5.72402E+12	1298938.88	1481712574	3863	62	**3870**	**4054**
6.66933E+12	1464632.45	1773992114	3760	61	**3935**	**4117**
7.5467E+12	1619739.84	2063046432	3658	60	**3982**	**4161**
8.34292E+12	1763477.76	2343591406	3560	60	**4014**	**4191**
9.0718E+12	1895991.3	2612581215	3472	59	**4038**	**4212**
9.70965E+12	2018047.54	2868816017	3385	58	**4050**	**4222**
1.02881E+13	2128797.72	3108129825	3310	58	**4060**	**4230**
1.08137E+13	2231169.56	3334951459	3243	57	**4066**	**4235**
1.1268E+13	2324130.74	3545484685	3178	56	**4067**	**4234**
1.1683E+13	2409231.71	3741946413	3122	56	**4068**	**4234**
1.20494E+13	2485951.36	3922060595	3072	55	**4068**	**4232**
1.23685E+13	2556513.19	4090191015	3024	55	**4064**	**4227**
1.26739E+13	2620254.44	4244078519	2986	55	**4064**	**4226**
1.29333E+13	2678754.16	4386968894	2948	54	**4061**	**4221**
1.31674E+13	2732706.55	4520142574	2913	54	**4057**	**4217**

Baseline continued

c mortality 25% decrease

	A	B	c	a+b	a+c	a+b+1	a+c+1	a+1	mle =($e12*$f12)/$b12	nue =[($g12*$h12)/$i12]	=$k12-1
1997	616	989	534	1605	1150	1606	1151	617	2996	2996	2995
1998	748	1234	661	1990	1437	1991	1438	749	3821	3820	3819
1999	865	1450	781	2339	1698	2340	1699	866	4590	4589	4588
2000	968	1646	891	2655	1937	2656	1938	969	5312	5311	5310
2001	1059	1824	991	2942	2155	2943	2156	1060	5988	5987	5986
2002	1139	1985	1083	3202	2354	3203	2355	1140	6619	6618	6617
2003	1209	2132	1167	3438	2536	3439	2537	1210	7210	7209	7208
2004	1272	2265	1243	3653	2702	3654	2703	1273	7762	7761	7760
2005	1327	2386	1313	3848	2854	3849	2855	1328	8276	8275	8274
2006	1376	2496	1377	4026	2993	4027	2994	1377	8757	8756	8755
2007	1420	2597	1436	4188	3121	4189	3122	1421	9207	9206	9205
2008	1458	2688	1489	4336	3237	4337	3238	1459	9626	9625	9624
2009	1493	2771	1539	4470	3345	4471	3346	1494	10017	10015	10014
2010	1524	2848	1584	4593	3443	4594	3444	1525	10380	10378	10377
2011	1551	2917	1626	4705	3534	4706	3535	1552	10719	10718	10717
2012	1576	2981	1664	4808	3617	4809	3618	1577	11037	11035	11034
2013	1598	3039	1699	4902	3694	4903	3695	1599	11332	11331	11330
2014	1618	3093	1731	4988	3764	4989	3765	1619	11606	11604	11603
2015	1636	3141	1761	5066	3829	5067	3830	1637	11859	11857	11856
2016	1652	3186	1789	5139	3889	5140	3890	1653	12097	12095	12094

=(a+b+1)(a+c+1)(b)(c)/(a+1)2 (a+2)
var NUE

					95% CI	
=($g12*$h12*$c12*$d12)	=$i12*$i12	=($b12+2)*$n12	=$m12/$o12	=SQRT($p12)	=$L12-1.96*$q12	=$L12+1.96*$q12
9.76244E+11	380689	235265802	4150	64	**2869**	**3121**
2.33501E+12	561660.314	421492365.7	5540	74	**3745**	**3965**
4.50326E+12	750562.323	651000230.4	6917	83	**4505**	**4751**
7.54963E+12	939368.024	911384250.7	8284	91	**5219**	**5488**
1.1473E+13	1123303.22	1191667454	9628	98	**5888**	**6178**
1.62153E+13	1298938.88	1481712574	10944	105	**6513**	**6822**
2.16949E+13	1464632.45	1773992114	12229	111	**7098**	**7425**
2.78035E+13	1619739.84	2063046432	13477	116	**7643**	**7987**
3.44186E+13	1763477.76	2343591406	14686	121	**8153**	**8512**
4.14346E+13	1895991.3	2612581215	15860	126	**8629**	**9002**
4.87521E+13	2018047.54	2868816017	16994	130	**9075**	**9461**
5.62144E+13	2128797.72	3108129825	18086	134	**9489**	**9888**
6.37946E+13	2231169.56	3334951459	19129	138	**9876**	**10285**
7.13571E+13	2324130.74	3545484685	20126	142	**10235**	**10655**
7.88891E+13	2409231.71	3741946413	21082	145	**10572**	**11001**
8.6295E+13	2485951.36	3922060595	22002	148	**10886**	**11325**
9.35613E+13	2556513.19	4090191015	22875	151	**11178**	**11626**
1.00578E+14	2620254.44	4244078519	23698	154	**11449**	**11905**
1.07362E+14	2678754.16	4386968894	24473	156	**11700**	**12163**
1.13967E+14	2732706.55	4520142574	25213	159	**11936**	**12406**

Baseline ends

SCENARIO 1: Increase acceptance by 10% at 10 years

a

									mle	**nue**	
	A	B	c	a+b	a+c	a+b+1	a+c+1	a+1	=($e12*$f12)/$b12	=[($g12*$h12)/$i12]	=$k12-1
1997	616	989	534	1605	1150	1606	1151	617	2996	2996	**2995**
1998	748	1205	646	1944	1404	1945	1405	749	3647	3646	**3645**
1999	867	1392	751	2245	1632	2246	1633	868	4225	4225	**4224**
2000	974	1559	845	2515	1837	2516	1838	975	4744	4744	**4743**
2001	1070	1709	931	2756	2023	2757	2024	1071	5211	5211	**5210**
2002	1157	1843	1008	2973	2192	2974	2193	1158	5634	5634	**5633**
2003	1236	1965	1079	3169	2346	3170	2347	1237	6017	6017	**6016**
2004	1307	2075	1144	3347	2487	3348	2488	1308	6367	6366	**6365**
2005	1373	2176	1203	3509	2616	3510	2617	1374	6686	6685	**6684**
2006	1433	2268	1258	3658	2735	3659	2736	1434	6979	6979	**6978**
2007	1489	2353	1309	3795	2846	3796	2847	1490	7251	7251	**7250**
2008	1541	2431	1357	3921	2949	3922	2950	1542	7503	7502	**7501**
2009	1589	2504	1400	4039	3044	4040	3045	1590	7736	7736	**7735**
2010	1634	2572	1442	4149	3134	4150	3135	1635	7955	7955	**7954**
2011	1677	2637	1480	4253	3218	4254	3219	1678	8161	8161	**8160**
2012	1717	2697	1517	4350	3298	4351	3299	1718	8356	8355	**8354**
2013	1755	2755	1552	4443	3373	4444	3374	1756	8540	8539	**8538**
2014	1791	2809	1585	4531	3446	4532	3447	1792	8716	8716	**8715**
2015	1826	2862	1617	4616	3515	4617	3516	1827	8885	8885	**8884**
2016	1860	2912	1648	4697	3582	4698	3583	1861	9048	9047	**9046**

Scenario 1 continued

=(a+b+1)(a+c+1)(b)(c)/(a+1)2
(a+2)
var NUE

					95% CI	
=($g12*$h12*$c12*$d12)	=$i12*$i12	=($b12+2)*$n12	=$m12/$o12	=SQRT($p12)	=$L12-1.96*$q12	=$L12+1.96*$q12
9.76244E+11	380689	235265802	4150	64	**2869**	**3121**
2.1272E+12	561660.314	421492365.7	5047	71	**3574**	**3785**
3.8325E+12	753753.876	655155331.6	5850	76	**4147**	**4373**
6.0933E+12	950313.026	927353462.9	6571	81	**4662**	**4902**
8.87303E+12	1146719.72	1229111535	7219	85	**5125**	**5377**
1.21217E+13	1340292.44	1553010258	7805	88	**5544**	**5806**
1.57751E+13	1529006.44	1892191341	8337	91	**5925**	**6195**
1.9775E+13	1711962.9	2241678456	8822	94	**6271**	**6549**
2.40481E+13	1887958.44	2595999495	9264	96	**6588**	**6873**
2.85647E+13	2057704.18	2953772621	9671	98	**6880**	**7171**
3.32897E+13	2221500.82	3313301829	10047	100	**7150**	**7446**
3.81549E+13	2378442.53	3670460079	10395	102	**7399**	**7701**
4.31357E+13	2529022.28	4024407870	10719	104	**7631**	**7937**
4.82478E+13	2674827.54	4377328521	11022	105	**7849**	**8160**
5.34502E+13	2815449.08	4726941932	11308	106	**8054**	**8368**
5.87301E+13	2951386.56	5073315444	11576	108	**8247**	**8565**
6.40857E+13	3083114.57	5416662333	11831	109	**8430**	**8752**
6.95649E+13	3212375.14	5760784455	12076	110	**8605**	**8930**
7.51189E+13	3338257.87	6102635826	12309	111	**8773**	**9101**
8.0771E+13	3461720.72	6444235450	12534	112	**8934**	**9266**

Scenario 1 continued

b mortality 50% increase

									mle	**nue**	
	A	B	c	a+b	a+c	a+b+1	a+c+1	a+1	=($e12*$f12)/$b12	=[($g12*$h12)/$i12]	=$k12-1
1997	616	989	534	1605	1150	1606	1151	617	2996	2996	**2995**
1998	748	1149	615	1853	1338	1854	1339	749	3313	3312	**3311**
1999	867	1277	689	2059	1497	2060	1498	868	3554	3554	**3553**
2000	974	1384	752	2232	1634	2233	1635	975	3745	3745	**3744**
2001	1070	1474	805	2378	1751	2379	1752	1071	3892	3892	**3891**
2002	1157	1552	853	2503	1854	2504	1855	1158	4012	4012	**4011**
2003	1236	1618	894	2610	1943	2611	1944	1237	4104	4105	**4104**
2004	1307	1677	931	2705	2023	2706	2024	1308	4186	4186	**4185**
2005	1373	1729	963	2788	2094	2789	2095	1374	4252	4252	**4251**
2006	1433	1775	993	2863	2158	2864	2159	1434	4310	4311	**4310**
2007	1489	1817	1020	2931	2217	2932	2218	1490	4363	4363	**4362**
2008	1541	1856	1045	2993	2271	2994	2272	1542	4410	4411	**4410**
2009	1589	1892	1068	3051	2321	3052	2322	1590	4456	4456	**4455**
2010	1634	1926	1090	3106	2369	3107	2370	1635	4502	4502	**4501**
2011	1677	1957	1110	3157	2413	3158	2414	1678	4543	4543	**4542**
2012	1717	1988	1129	3206	2455	3207	2456	1718	4584	4585	**4584**
2013	1755	2017	1148	3253	2496	3254	2497	1756	4627	4627	**4626**
2014	1791	2045	1166	3299	2535	3300	2536	1792	4669	4669	**4668**
2015	1826	2073	1184	3344	2573	3345	2574	1827	4712	4712	**4711**
2016	1860	2100	1200	3387	2609	3388	2610	1861	4752	4753	**4752**

=(a+b+1)(a+c+1)(b)(c)/(a+1)2
(a+2)
var NUE

					95% CI	
=($g12*$h12*$c12*$d12)	=$i12*$i12	=($b12+2)*$n12	=$m12/$o12	=SQRT($p12)	=$L12-1.96*$q12	=$L12+1.96*$q12
9.76244E+11	380689	235265802	4150	64	**2869**	**3121**
1.75538E+12	561660.314	421492365.7	4165	65	**3247**	**3438**
2.71273E+12	753753.876	655155331.6	4141	64	**3489**	**3680**
3.79754E+12	950313.026	927353462.9	4095	64	**3680**	**3870**
4.94967E+12	1146719.72	1229111535	4027	63	**3828**	**4016**
6.1475E+12	1340292.44	1553010258	3958	63	**3948**	**4134**
7.34118E+12	1529006.44	1892191341	3880	62	**4042**	**4226**
8.54773E+12	1711962.9	2241678456	3813	62	**4123**	**4306**
9.72863E+12	1887958.44	2595999495	3748	61	**4190**	**4371**
1.08955E+13	2057704.18	2953772621	3689	61	**4249**	**4429**
1.20519E+13	2221500.82	3313301829	3637	60	**4302**	**4480**
1.31866E+13	2378442.53	3670460079	3593	60	**4350**	**4527**
1.43124E+13	2529022.28	4024407870	3556	60	**4396**	**4572**
1.54527E+13	2674827.54	4377328521	3530	59	**4442**	**4618**
1.65627E+13	2815449.08	4726941932	3504	59	**4483**	**4658**
1.76804E+13	2951386.56	5073315444	3485	59	**4525**	**4699**
1.88154E+13	3083114.57	5416662333	3474	59	**4568**	**4742**
1.99606E+13	3212375.14	5760784455	3465	59	**4609**	**4784**
2.11281E+13	3338257.87	6102635826	3462	59	**4653**	**4827**
2.22855E+13	3461720.72	6444235450	3458	59	**4693**	**4867**

Scenario 1 continued

c mortality 25% decrease

									mle	**nue**	
	A	B	c	a+b	a+c	a+b+1	a+c+1	a+1	=($e12*$f12)/$b12	=[($g12*$h12)/$i12]	=$k12-1
1997	616	989	534	1605	1150	1606	1151	617	2996	2996	**2995**
1998	748	1234	661	1990	1437	1991	1438	749	3821	3820	**3819**
1999	867	1453	783	2344	1702	2345	1703	868	4600	4600	**4599**
2000	974	1655	896	2670	1948	2671	1949	975	5341	5340	**5339**
2001	1070	1842	1001	2971	2177	2972	2178	1071	6046	6045	**6044**
2002	1157	2015	1099	3250	2389	3251	2390	1158	6712	6711	**6710**
2003	1236	2176	1190	3509	2588	3510	2589	1237	7350	7349	**7348**
2004	1307	2324	1276	3749	2773	3750	2774	1308	7952	7950	**7949**
2005	1373	2463	1356	3973	2947	3974	2948	1374	8527	8526	**8525**
2006	1433	2593	1430	4183	3109	4184	3110	1434	9072	9071	**9070**
2007	1489	2715	1501	4379	3263	4380	3264	1490	9593	9592	**9591**
2008	1541	2830	1567	4564	3407	4565	3408	1542	10089	10088	**10087**
2009	1589	2938	1630	4738	3544	4739	3545	1590	10565	10564	**10563**
2010	1634	3039	1690	4902	3674	4903	3675	1635	11019	11017	**11016**
2011	1677	3136	1747	5058	3797	5059	3798	1678	11453	11451	**11450**
2012	1717	3228	1801	5206	3915	5207	3916	1718	11871	11869	**11868**
2013	1755	3316	1852	5348	4027	5349	4028	1756	12272	12271	**12270**
2014	1791	3399	1902	5483	4135	5484	4136	1792	12657	12655	**12654**
2015	1826	3480	1950	5613	4239	5614	4240	1827	13030	13028	**13027**
2016	1860	3557	1995	5737	4338	5738	4339	1861	13383	13381	**13380**

=(a+b+1)(a+c+1)(b)(c)/(a+1)2
(a+2)
var NUE

					95% CI	
=($g12*$h12*$c12*$d12)	=$i12*$i12	=($b12+2)*$n12	=$m12/$o12	=SQRT($p12)	=$L12-1.96*$q12	=$L12+1.96*$q12
9.76244E+11	380689	235265802	4150	64	**2869**	**3121**
2.33501E+12	561660.314	421492365.7	5540	74	**3745**	**3965**
4.54385E+12	753753.876	655155331.6	6936	83	**4516**	**4762**
7.7221E+12	950313.026	927353462.9	8327	91	**5248**	**5518**
1.19404E+13	1146719.72	1229111535	9715	99	**5945**	**6237**
1.72054E+13	1340292.44	1553010258	11079	105	**6605**	**6917**
2.35362E+13	1529006.44	1892191341	12439	112	**7237**	**7567**
3.08427E+13	1711962.9	2241678456	13759	117	**7832**	**8179**
3.91204E+13	1887958.44	2595999495	15070	123	**8403**	**8766**
4.82625E+13	2057704.18	2953772621	16339	128	**8942**	**9321**
5.82594E+13	2221500.82	3313301829	17583	133	**9458**	**9851**
6.89934E+13	2378442.53	3670460079	18797	137	**9950**	**10355**
8.04528E+13	2529022.28	4024407870	19991	141	**10422**	**10840**
9.2551E+13	2674827.54	4377328521	21143	145	**10871**	**11301**
1.05242E+14	2815449.08	4726941932	22264	149	**11301**	**11743**
1.18527E+14	2951386.56	5073315444	23363	153	**11715**	**12168**
1.32338E+14	3083114.57	5416662333	24432	156	**12113**	**12576**
1.46663E+14	3212375.14	5760784455	25459	160	**12495**	**12967**
1.61527E+14	3338257.87	6102635826	26468	163	**12864**	**13346**
1.76715E+14	3461720.72	6444235450	27422	166	**13215**	**13705**

SCENARIO 2: Increase acceptance by 30% every 10 years

a

									mle	**nue**	
	A	B	C	a+b	a+c	a+b+1	a+c+1	a+1	=($e12*$f12)/$b12	=[($g12*$h12)/$i12]	=$k12-1
1997	616	989	534	1605	1150	1606	1151	617	2996	2996	**2995**
1998	748	1205	646	1944	1404	1945	1405	749	3647	3646	**3645**
1999	867	1399	754	2256	1640	2257	1641	868	4266	4266	**4265**
2000	974	1578	856	2545	1860	2546	1861	975	4861	4860	**4859**
2001	1070	1745	951	2815	2067	2816	2068	1071	5439	5438	**5437**
2002	1157	1903	1041	3069	2263	3070	2264	1158	6004	6004	**6003**
2003	1236	2052	1127	3310	2449	3311	2450	1237	6561	6560	**6559**
2004	1307	2195	1209	3540	2628	3541	2629	1308	7116	7115	**7114**
2005	1373	2332	1288	3761	2800	3762	2801	1374	7670	7669	**7668**
2006	1433	2464	1365	3974	2968	3975	2969	1434	8228	8227	**8226**
2007	1489	2593	1440	4183	3131	4184	3132	1490	8793	8792	**8791**
2008	1541	2720	1514	4387	3291	4388	3292	1542	9368	9367	**9366**
2009	1589	2845	1587	4588	3449	4589	3450	1590	9957	9955	**9954**
2010	1634	2968	1658	4787	3605	4788	3606	1635	10558	10557	**10556**
2011	1677	3091	1730	4985	3761	4986	3762	1678	11180	11179	**11178**
2012	1717	3213	1801	5183	3916	5184	3917	1718	11821	11820	**11819**
2013	1755	3337	1873	5382	4072	5383	4073	1756	12488	12487	**12486**
2014	1791	3460	1945	5581	4228	5582	4229	1792	13173	13171	**13170**
2015	1826	3585	2018	5783	4386	5784	4387	1827	13890	13888	**13887**
2016	1860	3712	2091	5987	4546	5988	4547	1861	14636	14634	**14633**

=(a+b+1)(a+c+1)(b)(c)/(a+1)2
(a+2)
var NUE

					95% CI	
=($g12*$h12*$c12*$d12)	=$i12*$i12	=($b12+2)*$n12	=$m12/$o12	=SQRT($p12)	=$L12-1.96*$q12	=$L12+1.96*$q12
9.76244E+11	380689	235265802	4150	64	**2869**	**3121**
2.1272E+12	561660.314	421492365.7	5047	71	**3574**	**3785**
3.90816E+12	753753.876	655155331.6	5965	77	**4188**	**4416**
6.39669E+12	950313.026	927353462.9	6898	83	**4776**	**5022**
9.66388E+12	1146719.72	1229111535	7862	89	**5349**	**5611**
1.37672E+13	1340292.44	1553010258	8865	94	**5908**	**6187**
1.87539E+13	1529006.44	1892191341	9911	100	**6460**	**6754**
2.46999E+13	1711962.9	2241678456	11018	105	**7009**	**7320**
3.16477E+13	1887958.44	2595999495	12191	110	**7558**	**7884**
3.96998E+13	2057704.18	2953772621	13440	116	**8110**	**8454**
4.89479E+13	2221500.82	3313301829	14773	122	**8670**	**9029**
5.94801E+13	2378442.53	3670460079	16205	127	**9238**	**9615**
7.14502E+13	2529022.28	4024407870	17754	133	**9821**	**10216**
8.49764E+13	2674827.54	4377328521	19413	139	**10416**	**10829**
1.00297E+14	2815449.08	4726941932	21218	146	**11032**	**11463**
1.17542E+14	2951386.56	5073315444	23169	152	**11666**	**12117**
1.37038E+14	3083114.57	5416662333	25299	159	**12327**	**12797**
1.58863E+14	3212375.14	5760784455	27577	166	**13004**	**13495**
1.83555E+14	3338257.87	6102635826	30078	173	**13713**	**14227**
2.11346E+14	3461720.72	6444235450	32796	181	**14452**	**14988**

Scenario 2 continued

b mortality 50% increase

									mle	**nue**	
	A	B	c	a+b	a+c	a+b+1	a+c+1	a+1	=($e12*$f12)/$b12	=[($g12*$h12)/$i12]	=$k12-1
1997	616	989	534	1605	1150	1606	1151	617	2996	2996	**2995**
1998	748	1149	615	1853	1338	1854	1339	749	3313	3312	**3311**
1999	867	1283	692	2070	1505	2071	1506	868	3592	3592	**3591**
2000	974	1402	761	2262	1655	2263	1656	975	3844	3844	**3843**
2001	1070	1510	825	2435	1793	2436	1794	1071	4081	4081	**4080**
2002	1157	1608	883	2593	1920	2594	1921	1158	4304	4304	**4303**
2003	1236	1699	938	2741	2039	2742	2040	1237	4523	4524	**4523**
2004	1307	1786	990	2880	2153	2881	2154	1308	4743	4743	**4742**
2005	1373	1869	1040	3014	2261	3015	2262	1374	4963	4963	**4962**
2006	1433	1949	1088	3143	2366	3144	2367	1434	5188	5188	**5187**
2007	1489	2027	1136	3270	2469	3271	2470	1490	5420	5421	**5420**
2008	1541	2106	1183	3396	2571	3397	2572	1542	5665	5665	**5664**
2009	1589	2182	1229	3520	2671	3521	2672	1590	5916	5916	**5915**
2010	1634	2260	1275	3645	2772	3646	2773	1635	6182	6182	**6181**
2011	1677	2338	1322	3771	2873	3772	2874	1678	6461	6461	**6460**
2012	1717	2417	1368	3898	2974	3899	2975	1718	6752	6752	**6751**
2013	1755	2497	1415	4027	3077	4028	3078	1756	7061	7061	**7060**
2014	1791	2578	1463	4158	3181	4159	3182	1792	7384	7384	**7383**
2015	1826	2661	1512	4292	3287	4293	3288	1827	7726	7726	**7725**
2016	1860	2746	1561	4429	3394	4430	3395	1861	8084	8083	**8082**

=(a+b+1)(a+c+1)(b)(c)/(a+1)2
(a+2)
var NUE

					95% CI	
=($g12*$h12*$c12*$d12)	=$i12*$i12	=($b12+2)*$n12	=$m12/$o12	=SQRT($p12)	=$L12-1.96*$q12	=$L12+1.96*$q12
9.76244E+11	380689	235265802	4150	64	**2869**	**3121**
1.75538E+12	561660.314	421492365.7	4165	65	**3247**	**3438**
2.77116E+12	753753.876	655155331.6	4230	65	**3526**	**3719**
4.00115E+12	950313.026	927353462.9	4315	66	**3778**	**3972**
5.44162E+12	1146719.72	1229111535	4427	67	**4014**	**4210**
7.07539E+12	1340292.44	1553010258	4556	67	**4236**	**4436**
8.91607E+12	1529006.44	1892191341	4712	69	**4454**	**4657**
1.09743E+13	1711962.9	2241678456	4896	70	**4672**	**4879**
1.32548E+13	1887958.44	2595999495	5106	71	**4891**	**5103**
1.5783E+13	2057704.18	2953772621	5343	73	**5114**	**5330**
1.86036E+13	2221500.82	3313301829	5615	75	**5345**	**5567**
2.17563E+13	2378442.53	3670460079	5927	77	**5587**	**5815**
2.52272E+13	2529022.28	4024407870	6269	79	**5836**	**6070**
2.91344E+13	2674827.54	4377328521	6656	82	**6099**	**6341**
3.34966E+13	2815449.08	4726941932	7086	84	**6376**	**6625**
3.83506E+13	2951386.56	5073315444	7559	87	**6664**	**6921**
4.38144E+13	3083114.57	5416662333	8089	90	**6970**	**7236**
4.99214E+13	3212375.14	5760784455	8666	93	**7290**	**7565**
5.67939E+13	3338257.87	6102635826	9306	96	**7628**	**7914**
6.44778E+13	3461720.72	6444235450	10006	100	**7982**	**8279**

Scenario 2 continued

c mortality 25% decrease

									mle	**nue**	
	A	B	c	a+b	a+c	a+b+1	a+c+1	a+1	=($e12*$f12)/$b12	=[($g12*$h12)/$i12]	=$k12-1
1997	616	989	534	1605	1150	1606	1151	617	2996	2996	**2995**
1998	748	1234	661	1990	1437	1991	1438	749	3821	3820	**3819**
1999	867	1459	787	2354	1710	2355	1711	868	4642	4641	**4640**
2000	974	1675	907	2701	1971	2702	1972	975	5467	5466	**5465**
2001	1070	1880	1022	3032	2221	3033	2222	1071	6294	6293	**6292**
2002	1157	2076	1133	3349	2463	3350	2464	1158	7131	7130	**7129**
2003	1236	2266	1240	3655	2696	3656	2697	1237	7975	7974	**7973**
2004	1307	2450	1344	3951	2922	3952	2923	1308	8830	8829	**8828**
2005	1373	2628	1446	4239	3143	4240	3144	1374	9703	9702	**9701**
2006	1433	2802	1545	4520	3359	4521	3360	1434	10592	10590	**10589**
2007	1489	2974	1643	4796	3571	4797	3572	1490	11498	11496	**11495**
2008	1541	3142	1739	5067	3780	5068	3781	1542	12427	12425	**12424**
2009	1589	3308	1834	5335	3987	5336	3988	1590	13384	13381	**13380**
2010	1634	3473	1929	5601	4193	5602	4194	1635	14368	14366	**14365**
2011	1677	3636	2023	5865	4397	5866	4398	1678	15378	15375	**15374**
2012	1717	3800	2116	6129	4601	6130	4602	1718	16424	16421	**16420**
2013	1755	3964	2211	6393	4806	6394	4807	1756	17508	17505	**17504**
2014	1791	4128	2305	6658	5011	6659	5012	1792	18625	18621	**18620**
2015	1826	4294	2400	6925	5218	6926	5219	1827	19788	19784	**19783**
2016	1860	4460	2496	7194	5426	7195	5427	1861	20991	20987	**20986**

=(a+b+1)(a+c+1)(b)(c)/(a+1)2
(a+2)
var NUE

					95% CI	
=($g12*$h12*$c12*$d12)	=$i12*$i12	=($b12+2)*$n12	=$m12/$o12	=SQRT($p12)	=$L12-1.96*$q12	=$L12+1.96*$q12
9.76244E+11	380689	235265802	4150	64	**2869**	**3121**
2.33501E+12	561660.314	421492365.7	5540	74	**3745**	**3965**
4.62587E+12	753753.876	655155331.6	7061	84	**4556**	**4805**
8.09008E+12	950313.026	927353462.9	8724	93	**5371**	**5648**
1.29433E+13	1146719.72	1229111535	10531	103	**6190**	**6494**
1.94185E+13	1340292.44	1553010258	12504	112	**7017**	**7348**
2.77105E+13	1529006.44	1892191341	14645	121	**7852**	**8210**
3.80349E+13	1711962.9	2241678456	16967	130	**8697**	**9083**
5.06531E+13	1887958.44	2595999495	19512	140	**9561**	**9975**
6.57766E+13	2057704.18	2953772621	22269	149	**10439**	**10881**
8.3695E+13	2221500.82	3313301829	25260	159	**11336**	**11807**
1.04673E+14	2378442.53	3670460079	28518	169	**12255**	**12755**
1.29093E+14	2529022.28	4024407870	32077	179	**13201**	**13731**
1.57366E+14	2674827.54	4377328521	35950	190	**14175**	**14736**
1.89745E+14	2815449.08	4726941932	40141	200	**15174**	**15767**
2.26881E+14	2951386.56	5073315444	44720	211	**16208**	**16834**
2.6933E+14	3083114.57	5416662333	49723	223	**17281**	**17941**
3.17569E+14	3212375.14	5760784455	55126	235	**18385**	**19080**
3.72514E+14	3338257.87	6102635826	61042	247	**19536**	**20267**
4.34701E+14	3461720.72	6444235450	67456	260	**20726**	**21495**

SCENARIO 3: Increase acceptance by 50% every 10 years

a

									mle	**nue**	
	A	B	C	a+b	a+c	a+b+1	a+c+1	a+1	=($e12*$f12)/$b12	=[($g12*$h12)/$i12]	=$k12-1
1997	616	989	534	1605	1150	1606	1151	617	2996	2996	**2995**
1998	748	1205	646	1944	1404	1945	1405	749	3647	3646	**3645**
1999	867	1406	758	2267	1647	2268	1648	868	4306	4305	**4304**
2000	974	1598	866	2577	1883	2578	1884	975	4983	4982	**4981**
2001	1070	1784	972	2877	2112	2878	2113	1071	5680	5679	**5678**
2002	1157	1966	1075	3171	2337	3172	2338	1158	6407	6406	**6405**
2003	1236	2145	1178	3460	2560	3461	2561	1237	7169	7168	**7167**
2004	1307	2324	1280	3748	2782	3749	2783	1308	7975	7974	**7973**
2005	1373	2502	1382	4036	3004	4037	3005	1374	8830	8829	**8828**
2006	1433	2682	1485	4326	3229	4327	3230	1434	9745	9743	**9742**
2007	1489	2864	1590	4620	3456	4621	3457	1490	10720	10718	**10717**
2008	1541	3050	1696	4920	3688	4921	3689	1542	11773	11771	**11770**
2009	1589	3240	1806	5226	3925	5227	3926	1590	12906	12904	**12903**
2010	1634	3435	1917	5541	4168	5542	4169	1635	14130	14127	**14126**
2011	1677	3636	2032	5865	4418	5866	4419	1678	15452	15449	**15448**
2012	1717	3844	2151	6200	4676	6201	4677	1718	16885	16882	**16881**
2013	1755	4059	2274	6547	4944	6548	4945	1756	18445	18441	**18440**
2014	1791	4282	2402	6907	5221	6908	5222	1792	20131	20127	**20126**
2015	1826	4514	2535	7281	5510	7282	5511	1827	21970	21964	**21963**
2016	1860	4756	2672	7671	5809	7672	5810	1861	23963	23957	**23956**

=(a+b+1)(a+c+1)(b)(c)/(a+1)2
(a+2)
var NUE

					95% CI	
=($g12*$h12*$c12*$d12)	=$i12*$i12	=($b12+2)*$n12	=$m12/$o12	=SQRT($p12)	=$L12-1.96*$q12	=$L12+1.96*$q12
9.76244E+11	380689	235265802	4150	64	**2869**	**3121**
2.1272E+12	561660.314	421492365.7	5047	71	**3574**	**3785**
3.98011E+12	753753.876	655155331.6	6075	78	**4226**	**4457**
6.72168E+12	950313.026	927353462.9	7248	85	**4896**	**5148**
1.05384E+13	1146719.72	1229111535	8574	93	**5585**	**5859**
1.56741E+13	1340292.44	1553010258	10093	100	**6304**	**6602**
2.23912E+13	1529006.44	1892191341	11833	109	**7058**	**7380**
3.10266E+13	1711962.9	2241678456	13841	118	**7855**	**8204**
4.19473E+13	1887958.44	2595999495	16158	127	**8701**	**9077**
5.56793E+13	2057704.18	2953772621	18850	137	**9605**	**10011**
7.27446E+13	2221500.82	3313301829	21955	148	**10569**	**11007**
9.39437E+13	2378442.53	3670460079	25595	160	**11610**	**12084**
1.2005E+14	2529022.28	4024407870	29830	173	**12730**	**13242**
1.52182E+14	2674827.54	4377328521	34766	186	**13940**	**14491**
1.91562E+14	2815449.08	4726941932	40526	201	**15246**	**15842**
2.39798E+14	2951386.56	5073315444	47266	217	**16663**	**17307**
2.98913E+14	3083114.57	5416662333	55184	235	**18205**	**18900**
3.71007E+14	3212375.14	5760784455	64402	254	**19872**	**20623**
4.5917E+14	3338257.87	6102635826	75241	274	**21689**	**22501**
5.66484E+14	3461720.72	6444235450	87906	296	**23660**	**24537**

Scenario 3 continued

b mortality 50% increase

									mle	**nue**	
	A	B	c	a+b	a+c	a+b+1	a+c+1	a+1	=($e12*$f12)/$b12	=[($g12*$h12)/$i12]	=$k12-1
1997	616	989	534	1605	1150	1606	1151	617	2996	2996	**2995**
1998	748	1149	615	1853	1338	1854	1339	749	3313	3312	**3311**
1999	867	1290	696	2080	1513	2081	1514	868	3629	3629	**3628**
2000	974	1421	772	2292	1678	2293	1679	975	3949	3949	**3948**
2001	1070	1546	845	2493	1836	2494	1837	1071	4278	4278	**4277**
2002	1157	1667	915	2688	1990	2689	1991	1158	4624	4624	**4623**
2003	1236	1785	985	2879	2142	2880	2143	1237	4991	4991	**4990**
2004	1307	1903	1055	3069	2294	3070	2295	1308	5385	5385	**5384**
2005	1373	2022	1125	3261	2445	3262	2446	1374	5807	5807	**5806**
2006	1433	2142	1196	3455	2599	3456	2600	1434	6264	6264	**6263**
2007	1489	2265	1268	3654	2756	3655	2757	1490	6761	6761	**6760**
2008	1541	2392	1342	3858	2917	3859	2918	1542	7302	7302	**7301**
2009	1589	2522	1418	4068	3083	4069	3084	1590	7891	7891	**7890**
2010	1634	2658	1497	4287	3254	4288	3255	1635	8535	8534	**8533**
2011	1677	2798	1578	4513	3431	4514	3432	1678	9234	9233	**9232**
2012	1717	2945	1663	4750	3615	4751	3616	1718	10001	10000	**9999**
2013	1755	3098	1751	4996	3807	4997	3808	1756	10838	10837	**10836**
2014	1791	3257	1843	5253	4007	5254	4008	1792	11750	11749	**11748**
2015	1826	3424	1939	5522	4216	5523	4217	1827	12749	12747	**12746**
2016	1860	3598	2040	5804	4434	5805	4435	1861	13839	13837	**13836**

=(a+b+1)(a+c+1)(b)(c)/(a+1)2
(a+2)
var NUE

					95% CI	
=($g12*$h12*$c12*$d12)	=$i12*$i12	=($b12+2)*$n12	=$m12/$o12	=SQRT($p12)	=$L12-1.96*$q12	=$L12+1.96*$q12
9.76244E+11	380689	235265802	4150	64	**2869**	**3121**
1.75538E+12	561660.314	421492365.7	4165	65	**3247**	**3438**
2.82781E+12	753753.876	655155331.6	4316	66	**3562**	**3757**
4.2229E+12	950313.026	927353462.9	4554	67	**3881**	**4081**
5.98067E+12	1146719.72	1229111535	4866	70	**4208**	**4414**
8.16759E+12	1340292.44	1553010258	5259	73	**4551**	**4766**
1.08549E+13	1529006.44	1892191341	5737	76	**4915**	**5139**
1.41469E+13	1711962.9	2241678456	6311	79	**5304**	**5540**
1.81434E+13	1887958.44	2595999495	6989	84	**5722**	**5970**
2.30118E+13	2057704.18	2953772621	7791	88	**6175**	**6436**
2.89415E+13	2221500.82	3313301829	8735	93	**6666**	**6943**
3.61417E+13	2378442.53	3670460079	9847	99	**7201**	**7495**
4.48855E+13	2529022.28	4024407870	11153	106	**7784**	**8097**
5.55298E+13	2674827.54	4377328521	12686	113	**8420**	**8754**
6.84139E+13	2815449.08	4726941932	14473	120	**9112**	**9468**
8.41327E+13	2951386.56	5073315444	16583	129	**9870**	**10251**
1.03219E+14	3083114.57	5416662333	19056	138	**10698**	**11107**
1.26414E+14	3212375.14	5760784455	21944	148	**11600**	**12038**
1.54641E+14	3338257.87	6102635826	25340	159	**12587**	**13058**
1.88959E+14	3461720.72	6444235450	29322	171	**13665**	**14172**

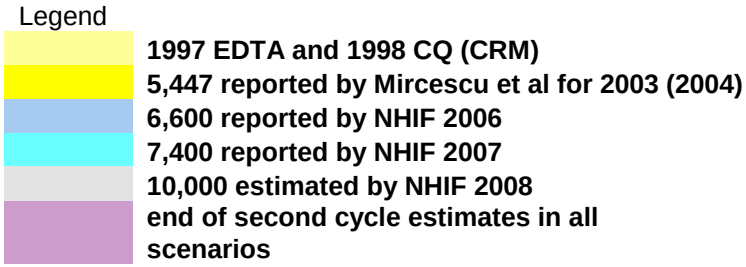
Scenario 3 continued

c mortality 25% decrease

									mle	**nue**	
	A	B	c	a+b	a+c	a+b+1	a+c+1	a+1	=($e12*$f12)/$b12	=[($g12*$h12)/$i12]	=$k12-1
1997	616	989	534	1605	1150	1606	1151	617	2996	2996	**2995**
1998	748	1234	661	1990	1437	1991	1438	749	3821	3820	**3819**
1999	867	1466	790	2365	1718	2366	1719	868	4685	4685	**4684**
2000	974	1694	917	2732	1994	2733	1995	975	5594	5593	**5592**
2001	1070	1918	1043	3094	2267	3095	2268	1071	6556	6555	**6554**
2002	1157	2141	1168	3453	2539	3454	2540	1158	7579	7578	**7577**
2003	1236	2362	1293	3810	2811	3811	2812	1237	8668	8667	**8666**
2004	1307	2584	1418	4168	3083	4169	3084	1308	9828	9827	**9826**
2005	1373	2807	1545	4528	3358	4529	3359	1374	11074	11072	**11071**
2006	1433	3034	1673	4893	3636	4894	3637	1434	12411	12408	**12407**
2007	1489	3263	1803	5263	3919	5264	3920	1490	13848	13845	**13844**
2008	1541	3497	1935	5640	4207	5641	4208	1542	15395	15392	**15391**
2009	1589	3736	2071	6025	4502	6026	4503	1590	17067	17063	**17062**
2010	1634	3981	2210	6421	4804	6422	4805	1635	18872	18868	**18867**
2011	1677	4233	2353	6827	5116	6828	5117	1678	20828	20823	**20822**
2012	1717	4493	2501	7247	5436	7248	5437	1718	22944	22938	**22937**
2013	1755	4762	2653	7681	5768	7682	5769	1756	25246	25239	**25238**
2014	1791	5041	2811	8130	6111	8131	6112	1792	27735	27728	**27727**
2015	1826	5329	2975	8595	6467	8596	6468	1827	30439	30430	**30429**
2016	1860	5629	3145	9079	6837	9080	6838	1861	33380	33371	**33370**

=(a+b+1)(a+c+1)(b)(c)/(a+1)2
(a+2)
var NUE

					95% CI	
=($g12*$h12*$c12*$d12)	=$i12*$i12	=($b12+2)*$n12	=$m12/$o12	=SQRT($p12)	=$L12-1.96*$q12	=$L12+1.96*$q12
9.76244E+11	380689	235265802	4150	64	**2869**	**3121**
2.33501E+12	561660.314	421492365.7	5540	74	**3745**	**3965**
4.71297E+12	753753.876	655155331.6	7194	85	**4599**	**4850**
8.47106E+12	950313.026	927353462.9	9135	96	**5496**	**5779**
1.40419E+13	1146719.72	1229111535	11424	107	**6447**	**6764**
2.19364E+13	1340292.44	1553010258	14125	119	**7458**	**7810**
3.27333E+13	1529006.44	1892191341	17299	132	**8534**	**8923**
4.71191E+13	1711962.9	2241678456	21020	145	**9681**	**10110**
6.59704E+13	1887958.44	2595999495	25412	159	**10911**	**11383**
9.03142E+13	2057704.18	2953772621	30576	175	**12233**	**12750**
1.21384E+14	2221500.82	3313301829	36635	191	**13652**	**14219**
1.60632E+14	2378442.53	3670460079	43764	209	**15181**	**15801**
2.09915E+14	2529022.28	4024407870	52160	228	**16834**	**17510**
2.71468E+14	2674827.54	4377328521	62017	249	**18618**	**19355**
3.48032E+14	2815449.08	4726941932	73627	271	**20550**	**21353**
4.42756E+14	2951386.56	5073315444	87272	295	**22642**	**23516**
5.59973E+14	3083114.57	5416662333	103380	322	**24917**	**25869**
7.04173E+14	3212375.14	5760784455	122236	350	**27377**	**28412**
8.81383E+14	3338257.87	6102635826	144427	380	**30049**	**31174**
1.09918E+15	3461720.72	6444235450	170568	413	**32957**	**34179**


Legend
1997 EDTA and 1998 CQ (CRM)
5,447 reported by Mircescu et al for 2003 (2004)
6,600 reported by NHIF 2006
7,400 reported by NHIF 2007
10,000 estimated by NHIF 2008
end of second cycle estimates in all scenarios

APPENDIX 12

List of acronyms

ACEI	**Angiotensin Converting Enzyme Inhibitor**
ADPKD	**Autosomal Dominant Polycystic Kidney Disease**
BMI	**Body Mass Index**
BUN	**Blood Urea Nitrogen**
CADTx	**Cadaver Donor Transplant**
CAPD	**Continuous Ambulatory Peritoneal Dialysis**
CBA	**Cost Benefit Analysis**
CBR	**Cost Benefit Ratio**
CCPD	**Continuous Cyclical Peritoneal Dialysis**
CEA	**Cost Effectiveness Analysis**
CER	**Cost Effectiveness Ratio**
CGN	**Chronic Glomerulonephritis**
CHD	**Coronary Heart Disease**
CKD	**Chronic Kidney Disease**
CRF	**Chronic Renal Failure**
CRI	**Chronic Renal Insufficiency**
CRM	**Capture-Recapture Method**
CUA	**Cost Utility Analysis**
CVD	**Cardio Vascular Disease**
DM	**Diabetes Mellitus**
ERA-EDTA	**European Renal Association- European Dialysis and Transplant Association**
EPO	**Erythropoietin**
ER	**Emergency Room**
ESRD	**End-Stage Renal Disease**
ESRF	**End-Stage Renal Failure**
FY	**Fiscal Year**
e-GFR	**Estimated-Glomerular Filtration Rate**
GN	**Glomerulonephritis**
GP	**General Practitioner**
Hb	**Haemoglobin**
HD	**Haemodialysis**
HDF	**Haemo-dia-filtration**
HHD	**Home Haemodialysis**
HLA	**Human Leukocyte Antigen**
HRQOL	**Health Related Quality of Life**

HT	**Hypertension**
ICD-9 or 10	**International Classification of Diseases 9th or 10th version**
ICER	**Incremental Cost-Effectiveness Ratio**
IDDM	**Insulin Dependent Diabetes Mellitus**
IPD	**Intermittent Peritoneal Dialysis**
JNC VI	**Joint National Committee on Hypertension 6th revision**
KDQ	**Kidney Disease Questionnaire**
KDQOL	**Kidney Disease Quality of Life**
KPS	**Karnofsky Performance Scale**
LRDTx	**Living Related Donor Transplant**
LYG	**Life Years Gained**
MDRD	**Modification of Diet in Renal Disease (Study)(USA)**
MI	**Myocardial Infarction**
MLE	**Maximum Likelihood Estimate**
MoH	**Ministry of Health**
MPGN	**Membrano-proliferative glomerulo-nephritis**
N or n	**Number of observed/ defined values**
NHANES	**National Health and Nutrition Examination Survey (USA)**
NHIF	**National Health Insurance Fund**
NHP	**Nottingham Health Profile**
NIDDM	**Non-Insulin Dependent Diabetes Mellitus**
NUE	**Nearly Unbiased Estimate**
OR	**Odds Ratio**
PRCV	**Packed Red Cells Volume**
PD	**Peritoneal Dialysis**
Pmp	**per million population**
PRD	**Primary Renal Disease**
PTFE	**Poly-Tetra-Fluoro-Ethylen (graft)**
PVD	**Peripheral Vascular Disease**
QALY	**Quality Adjusted Life Year**
QI	**Quetelet Index**
QOL	**Quality of Life**
QWB	**Quality of Well Being (Index)**
RCT	**Randomised Controlled Trial**
RQLP	**Renal Quality of Life Profile**
RR	**Risk Rate; Risk Ratio; Rate Ratio (contextual)**
RRT	**Renal Replacement Therapy**

SF-36	**Short Form- 36 Questionnaire**
SAR	**Standardised Acceptance Ratio**
SIP	**Sickness Impact Profile**
SSR	**Standardised Stock Ratio**
Tx	**Transpalant**
U	**Unit of measure (e.g. IU: international unit)**
UK	**United Kingdom**
USRDS	**United States Renal Data System**
VAS	**Visual Analogue Scale**
WHO	**World Health Organisation**