Universidade de Aveiro Departamento de Ciências Médicas

Ano 2019

Serafim Miguel de Sousa Barreto Guimarães

Medidas de resultados auto relatadas por doentes renais crónicos: análise de indicadores de experiência da doença crónica

Patient Reported Outcome Measures in Chronic Kidney Disease: analysis of self-reported indicators of experiencing chronic disease

Tese apresentada à Universidade de Aveiro para cumprimento dos requisitos necessários à obtenção do grau de Doutor em Ciências e Tecnologias da Saúde – Especialização em Decisão Clínica, realizada sob a orientação científica do Professor Doutor Nelson Fernando Pacheco da Rocha, Professor Catedrático da Universidade de Aveiro e co-orientação do Doutor Pedro Miguel Ferreira de Sá Couto, Professor Auxiliar do Departamento de Matemática, da Universidade de Aveiro

Ano 2019

Universidade de Aveiro Departamento de Ciências Médicas

Ano 2019

Júri

Presidente

Professor Doutor Joaquim Arnaldo Carvalho Martins
Professor Catedrático da Universidade de Aveiro

Vogais

Professora Doutora Anabela Soares Rodrigues,
Professora Associada Convidada da Universidade do Porto

Professor Doutor José António Machado Lopes
Professor Auxiliar Convidado da Universidade de Lisboa

Professor Doutor Francisco Luís Maia Mamede Pimentel
Investigador da Universidade de Coimbra

Professora Doutora Helena Sofia Silva Salgado Fonseca
Professora Auxiliar da Universidade Católica Portuguesa

Professor Doutor Nelson Fernando Pacheco da Rocha
Professor Catedrático da Universidade de Aveiro (orientador)

Agradecimento

Quando se chega ao fim de uma empresa como esta, impõe-se reconhecer que se chega ao fim carregado de muitas dívidas de gratidão a muitas pessoas que contribuíram para o seu resultado. Importa, por isso, fazer alguns agradecimentos.

Desde logo, agradeço aos meus Pais. Porque permitiram que eu existisse e crescesse e me dedicaram o melhor deles para eu ser quem sou. Porque, através do exemplo, me incutiram honestidade, disciplina e ambição. E porque me deram as ferramentas para singrar.

Também agradeço à restante família, do Porto, da Feira e de Lisboa, que constitui um estímulo e uma responsabilidade representar.

Depois, é essencial referir o Professor Doutor Luís Almeida. Com ele estou sempre a aprender. É uma fonte infindável de inspiração, sabedoria e capacidade de trabalho. É um prazer acompanhá-lo em aventuras de aprendizagem, organização e alegria no sucesso. Acredito que ainda teremos um longo caminho juntos. "Work Hard, Dream Big"!

Também agradeço aos meus orientadores, Professor Doutor Nelson Rocha, e Doutor Pedro Sá Couto. Foram tolerantes com as minhas ausências, e eficazes nas suas ajudas, essenciais para levar tudo isto a bom porto. Ambos tiveram a generosidade de entrar num comboio em andamento, a paciência para embrenhar-se num assunto estranho e a empatia para compreender as inquietações que me trouxeram a este tema. Não tenho palavras para lhes agradecer o seu apoio e orientação, com os inputs certos nos momentos certos. A tese não era a mesma sem os seus contributos.

Durante o trabalho de campo, as Dras. Hilma Caravau e Alina Ferreira recolheram com muita paciência, eficácia e eficiência os dados dos doentes. Também elas sentiram o que é uma consulta de Nefrologia à segunda feira de manhã, num hospital publico português. Sem o seu trabalho, esta tese simplesmente não existiria. Muito obrigado!

I also thank you very much, Bill Kilgallon and Amelia Fairburn-Beech, because you have reviewed in two days an "almost final" version of the work. It was fun to discover that I was still using English words from the time of Shakespeare. It's a pleasure to be your friend and I hope that we do much work together in the future.

Não me podia esquecer dos meus professores, porque não é possível construir sobre o vazio. De todos gostaria de destacar três: o Dr. Rui Seca, que já não está entre nós, e me ensinou a ver doentes e a fazer histórias clínicas; o Prof. Dr. José Teixeira Gomes, que orientou o meu primeiro trabalho publicado, ainda na faculdade, e a minha professora primária, Manuela Araújo, que também já partiu, a quem tanto devo, que olharia certamente com muito orgulho para este trabalho como olhou para todas as etapas da minha vida. A todos a minha gratidão.

Os meus colegas de trabalho merecem também um agradecimento, pela menor disponibilidade ou por dias mais tensos.

Refiro-me especialmente a todos os colegas da Blueclinical. Seria fastidioso enumerá-los a todos e seria injusto se me esquecesse de algum(a).

E também para todos, na Caledial, um agradecimento extensivo a todos os que, no dia a dia, fazem dela "a melhor clínica de hemodiálise do mundo". Destes, não posso deixar de destacar as nefrologistas Sónia Sousa, Clara Santos, Cátia Cunha e Sara Daniela Rodrigues, o Enfº Anselmo Madureira e a Cláudia Lima. Sem todos eles as coisas teriam sido bem mais complicadas. Prometo que agora vou ter mais tempo.

Em várias etapas do caminho, vários amigos interessaram-se e contribuíram, de forma pontual ou prolongada, recolhendo alguns dados, revendo fragmentos, propondo métodos, fornecendo aquela referência bibliográfica que faltava, ensinando-me os truques do Word, elogiando (mesmo quando não havia motivo para isso), ouvindo as minhas dúvidas e angústias, cuidando da minha forma física ou do meu humor, ou simplesmente estando disponíveis, e muitas outras colaborações, todas sempre muito valiosas. Agradeço a todos pela sua disponibilidade, pelo estímulo e pelo entusiasmo a: Susana Pereira, Jesus Garrido, Catarina Ribeiro, Inês Ladeira, Pedro Malta, Sophie Bento, Rute Lemos, Joaquim Pinheiro, Sofia Salgado, Isabel Fonseca, Marina Reis, Anabela Mota, Manuel Magalhães, Vera Gomes, José Luís Reis, Cristina Lopes, Rita Campos, Gil Costa e aos grupos da Bacelar e "Mini-Tertulianos".

Finalmente, aos mais importantes. Procurei não lhes faltar muito, em tempo ou atenção, mas sei que isto tem sempre custos. À Margarida, ao Miguel, ao João e, claro, à Joaninha, muito obrigado por tudo isto e por muito mais: por tudo.

Dedicatória Aos meus doentes, porque sem eles nada disto faria sentido.

Palavras-Chave

Indicadores-chave de desempenho (KPI);
Doença Renal Crónica (DRC);
Gestão da doença crónica;
Medidas de desempenho relatadas pelos doentes (PROM);
Bem-estar;
Qualidade de vida;
Modelo conceptual;
Resultados substitutos;
Quadro de resultados clínicos;
Short Physical Performance Battery (SPPB);
World Health Organization Disability Assessment Schedule (WHODAS);
Satisfaction with Life (SWLS);
Kidney Disease Quality of Life (KDQoL)

Resumo

Há frequentemente uma discrepância entre os dados clínicos, incluindo análises laboratoriais, e a experiência de se estar doente. O objetivo deste trabalho foi procurar indicadores-chave de desempenho de doença para além dos dados numéricos habituais. Como modelo de investigação, utilizamos a Doença Renal Crónica (DRC). Esses indicadores devem traduzir a experiência de viver com a doença e serem sensíveis às decisões médicas, para que possam ser alvo de intervenção. No capítulo 2, é feita uma contextualização da DRC, apresentando-se uma extensa lista dos indicadores que actualmente orientam as decisões dos médicos. No capítulo 3, faz-se uma abordagem geral das doenças crónicas, destacando modelos de gestão da doença crónica. Alguns indicadores actualmente usados também são referidos.

O trabalho experimental é apresentado no capítulo 4. A nossa hipótese baseou-se num modelo conceptual que postulava que uma determinada medida de resultados auto-relatados pelos doentes (PROM: Patient Reported Outcome Measures) seria adequada para uso diário em contexto clínico se tivesse uma correlação estatisticamente significativa entre os preditores (variáveis demográficas, índices de comorbilidade, estimativas de Taxa de Filtração Glomerular - TFGe - e eventos adversos do ano anterior) e os resultados (morte, diálise, hospitalizações e idas ao serviço de urgência), servindo assim como indicador de bem-estar. Realizámos um estudo observacional, tendo recrutado 60 doentes renais crónicos que responderam a vários questionários de PROM: "Short Physical Performance Battery" (SPPB), "World Health Organization Disability Assessment Schedule" (WHODAS), "Satisfaction With Life Scale" (SWLS) e "Kidney Disease Quality of Life" (KDQoL). O período de acompanhamento foi de 24 meses. Finalmente, estudámos a relevância dos resultados para os doentes. Para isso, foi-lhes pedido que classificassem seis desfechos, de acordo com o que acham que deveria ser a prioridade do seu médico ("evitar a morte", "evitar a diálise", "evitar o agravamento dos exames laboratoriais", "evitar a deterioração do seu estado geral", "evitar internamentos hospitalares" e "evitar idas ao serviço de urgência").

Os resultados permitiram concluir que: **1)** O SPPB previu morte, diálise e hospitalizações. **2)** O WHODAS previu morte e diálise. **3)** O domínio Função Física do KDQoL previu morte e hospitalizações. **4)** O domínio Saúde Mental do KDQoL previu morte. **5)** O domínio Energia/vitalidade do KDQoL previu hospitalizações. **6)** O domínio físico do KDQoL previu diálise. **7)** Domínio de Saúde Mental do KDQoL previu hospitalizações e idas ao serviço de urgência. **8)** Os domínios Dor, Função Social e Saúde Geral do KDQoL, bem como o SWLS não foram úteis na previsão de nenhum dos resultados propostos. **9)** A fórmula de Cockcroft-Gault (CG) para calcular a TFGe é a única que previu a morte. **10)** Todas as fórmulas de cálculo da TFGe previram o início da diálise. **11)** Apenas a fórmula de CG pôde prever a pontuação de algumas escalas do PROM: SPPB, domínio da Função Física do KDQoL e WHODAS. **12)** Ambas as escalas de comorbilidade de Charlson (de 1987 e 2011) são úteis para a predição dos resultados estudados: a primeira prevê mortes e internamentos hospitalares, enquanto a segunda prediz morte, diálise, hospitalizações e idas ao serviço de urgência. **13)** A principal prioridade dos doentes é que a principal preocupação do seu médico seja "evitar a morte", enquanto as opções "evitar diálise" e "evitar o agravamento dos exames laboratoriais" vêm a seguir, empatadas. **14)** Os doentes classificaram as opções "evitar hospitalização" e "evitar episódios de urgência" nos últimos lugares, depois de todas as demais.

Finalmente, **15)** O modelo conceptual proposto permitiu identificar oito possibilidades diferentes de relação entre preditores, PROM e resultados. Quatro deles mostraram ter utilidade clínica. São necessários estudos longitudinais com PROM para reforçar o seu papel no consultório e na enfermaria, e também na gestão da doença.

Keywords

Key Performance Indicators (KPI);
Chronic Kidney Disease (CKD);
Chronic Disease Management;
Patient Reported Outcome Measures (PROM),
Well-being;
Quality of Life;
Conceptual model;
Surrogate Outcomes;
Clinical Balanced Scorecard;
Short Physical Performance Battery (SPPB);
World Health Organization Disability Assessment Schedule (WHODAS);
Satisfaction With Life Scale (SWLS);
Kidney Disease Quality of Life (KDQoL)

Abstract

There is often a discrepancy between clinical data, including laboratory tests, and the patients' experience of being ill. The goal of this work was to search for Key Performance Indicators (KPI) of disease other than the usual numeric data. As research model, we have used Chronic Kidney Disease (CKD). Those indicators should express the experience of living with the disease and be sensible to medical decisions so that they can be targeted for intervention. In chapter 2, a contextualization of CKD is made, presenting an extensive list of the standard indicators that currently drive physicians' decisions. A general approach to chronic diseases is presented in chapter 3, highlighting models of interventions. Some existing indicators are also covered.

The experimental work is presented in chapter 4. Our hypothesis was based on a conceptual model which postulated that a given Patient Reported Outcome Measure (PROM) would be suitable for daily use in the clinical context provided that it would link predictors (demographic variables, comorbidity indices, estimates of Glomerular Filtration Rate – eGFR - and untoward events of the previous year) to Endpoints (death, dialysis, hospitalizations and emergency episodes) with statistically significant relationships and serve as indicator as surrogate of well-being. We conducted an observational study and recruited 60 patients with CKD to whom several questionnaires of PROM were administered: Short Physical Performance Battery (SPPB), World Health Organization Disability Assessment Schedule (WHODAS), Satisfaction With Life Scale (SWLS) and Kidney Disease Quality of Life (KDQoL). Follow-up period was 24 months. Lastly, we wanted to know the relevancy of the endpoints to the patients. For that, they were asked to rank six endpoints according to what they think their physician's priority should be (avoid death, avoid dialysis, avoid worsening of lab tests, prevent further deterioration of medical condition, avoid hospital admissions and avoid emergency episodes).

We conclude that: **1)** SPPB could predict death, dialysis and hospital admissions. **2)** WHODAS could predict death and dialysis. **3)** Physical Functioning domain of KDQoL could predict death and hospital admissions. **4)** Role Emotional domain of KDQoL could predict death. **5)** Energy/Vitality domain of KDQoL could predict hospital admissions. **6)** Role Physical domain of KDQoL could predict dialysis. **7)** Mental Health domain of KDQoL could predict hospital admissions and emergency episodes. **8)** Pain, Social Function and General Health domains of KDQoL, and SWLS were not useful in predicting any of the proposed endpoints. **9)** The Cockcroft-Gault (CG) formula to compute eGFR is the only that could predict mortality. **10)** All eGFR formulae predicted beginning of dialysis. **11)** Only the CG formula could predict the scores of some PROM scales: SPPB, Physical Function domain of KDQoL and WHODAS. **12)** Both the Charlson comorbidity scales (1987 and 2011) are useful for the prediction of studied endpoints: the first predicts death and hospital admissions while the second predicted mortality, dialysis, hospitalizations and emergency episodes. **13)** The highest priority of patients is that their physician's main concern should be to "Avoid death" whereas options "Avoid dialysis" and "Avoid worsening of laboratory tests" came next, in a tie. **14)** Patients ranked "Avoid hospitalization" and "Avoid emergency episodes" in the last places, after all the others.

Finally, **15)** Eight possible schemes were drawn from the analysis of the conceptual model. Four of them have shown to have clinical utility. Longitudinal exploration of these PROM is needed in order to reinforce their clear place at office and bedside and in disease management.

"Ignoranti, quem portum petat, nullus suus ventus est."
(For someone who doesn't know where he's sailing to, no wind is favourable)
Lucius Annaeus Seneca (Séc I d.C.)

"If you can't measure it, you can't improve it."
Peter Drucker (1909-2005)

Table of Contents

List of Annexes

- Authorization of the Board of the Hospital
- Authorization of the local Ethics Committee
- Authorization of the National Data Protection Commission
- Informed Consent Form
- Initial questionnaire for patients' characterization
- Questionnaire on patients' priorities
- Short Physical Performance Battery form
- World Health Organization Disability Assessment Schedule 2.0 form
- Satisfaction With Life Scale form
- Kidney Disease Quality of Life version 1.3 form

Index of tables

Index of Figures

Abbreviations

μmol/L	Micromole per litre
ADL	Activities of Daily Living
ADMA	Asymmetric dimethylarginine
AKI	Acute Kidney Injury
avg	Average (mean)
BMI	Body Mass Index
BSC	Balanced Scorecard
CDC	United States Centers for Disease Control and Prevention
CKD	Chronic Kidney Disease
CNPD	Comissão Nacional de Proteção de Dados (National Data Protection Commission)
COPD	Chronic Obstructive Pulmonary Disease
DALY	Disability Adjusted Life Year
DBMA	Disease Burden Management Assessment
ECOG	Eastern Cooperative Oncology Group
eGFR	Estimated Glomerular Filtration Rate
ER	Emergency Room
ERA-EDTA	European Renal Association - European Dialysis and Transplant Association
ESRD	End-Stage Renal Disease
FDA	Food and Drug Administration
GFR	Glomerular Filtration Rate
HDL	High Density Lipoproteins Cholesterol
HR	Hazard Ratio
HRQoL	Health Related Quality of Life
KDIGO	Kidney Disease Improving Global Outcomes
KDOQI	Kidney Disease Outcomes Quality Initiative
KDQoL	Kidney Disease Quality of Life
KDQoL _GH	Kidney Disease Quality of Life (General Health domain)
KDQoL _MH	Kidney Disease Quality of Life (Mental Health domain)
KDQoL _Pain	Kidney Disease Quality of Life (Pain domain)
KDQoL _PF	Kidney Disease Quality of Life (Physical Function domain)
KDQoL _RE	Kidney Disease Quality of Life (Role Emotional domain)
KDQoL _RP	Kidney Disease Quality of Life (Role Physical domain)

KDQoL _SF	Kidney Disease Quality of Life (Social Function domain)
KDQoL _VT	Kidney Disease Quality of Life (Vitality/Energy domain)
KF	Kidney Function
KIM-1	Kidney injury molecule-1
KPI	Key Performance Indicator
KPS	Karnofsky Performance Scale
L-FABP	Liver-type fatty acid binding protein
LDL-C	Low Density Lipoproteins Cholesterol
MDRD	Modification of Diet in Renal Disease study
MDRD4	Modification of Diet in Renal Disease study (formula with 4 variables)
MDRD6	Modification of Diet in Renal Disease study (formula with 6 variables)
mL/min	Millilitre per minute
MMS	Mini Mental State
MOS	Medical Outcomes Study
n	Number (count)
NGAL	Neutrophil gelatinase-associated lipocalin
NHANES	National Health and Nutrition Examination Survey
NHS	National Health Service (UK)
NIH	National Institute of Health
NKF	National Kidney Foundation
p.m.p.	Per million population (per million inhabitants)
PRO	Patient Reported Outcomes
PROM	Patient Reported Outcome Measures
PROMIS	Patient Reported Outcome Measures Information System
QALY	Quality Adjusted Life Year
QoL	Quality of Life
RRT	Renal Replacement Therapy
sd	Standard Deviation
SIP	Sickness Impact Profile
SLE	Systemic Lupus Erythematous
TTO	Time Trade-off
UK	United Kingdom
US	United States (of America)
USA	United States of America
WHO	World Health Organization
WHODAS	World Health Organization Disability Assessment Schedule

1 Introduction

1.1 Scope of the Problem

Nephrology earned its independence as a medical speciality with the introduction of dialysis to chronic kidney patients in March 1960, in Seattle, USA [1]. Since then, millions of patients have had their lives artificially extended thanks to machines that replace their lost kidney function. In spite of being a very severe disease, many of them have been able to lead an almost normal, productive existence with personal achievements both on the personal and at the social level, working, building a family, creating artistic work and enjoying life.

Nevertheless, living with dialysis poses a significant burden on a person's life, impacting considerably on well-being. This is a paradox, because of the extensive rehabilitation that patients get, which makes them feel well enough to dream a life without the need of this imprisoning therapy, creating negative feelings of indignation, frustration and, ultimately, depression [2 3]. Moreover, the patients rarely live long enough to complete the mourning cycle of resignation and often die in anger or depression.

The initiation of dialysis is a dramatic moment in patients' lives [4 5]. If they still in employment or not, their existence will subsequently be conditioned by the obligation of going to a dialysis clinic three times a week and stay there for four hours in the same position. The alternative, peritoneal dialysis, is not burden-free: three or four pauses in daily routine for a 30 to 40-minute operation which is not risk free either. Alternatively, sleeping every night connected to a machine that performs the exchanges. Some symptoms that they will experience will be due to dialysis, but most emerge from the simultaneous and continuous loss of residual kidney function, expressed as worsening of their health status, or are due to comorbidities, namely cardiovascular complications, which are particularly health limiting and the principal cause of death. Even so, all the blame will go to the treatment. Patients often get depressed, other concomitant diseases become evident and the general well-being suffers. in spite of a high standard quality care and support, it is far from being a comfortable experience for the patient. Some have compared it to living with

a cancer, as far as symptom burden and impairment of quality of life are related [6]. Unfortunately, it is the only chance they have to stay alive.

On the other hand, in developed countries, there is almost free access to dialysis, which is currently offered to many patients who would not have been considered suitable during the early decades of outpatient dialysis practice. Furthermore, patients are older, have more comorbidities and it is pertinent to challenge the option of proposing a Renal Replacement Therapy (RRT) to every patient that presents end stage renal failure [7].

Conservative treatment has emerged as an alternative option to RRT [8]. Some extreme cases offer little doubt about candidacy to RRT: absence of relationship with the world, advanced metastatic disease, very elderly frailty and advanced incurable diseases that lead to great functional limitations. These are some examples of situations in which little doubt rests on how the patient will benefit from RRT. However, there are other cases that, being less obvious, pose serious problems for decision making, especially when there is resistance of the patient or when patients present other comorbid conditions [9].

The role of the physician is to give counselling, which is based on a prediction of how the patient will cope and lead a life with an acceptable well-being. The key decision of proceeding or not to chronic dialysis therapy is a topic for which there will never be a randomized controlled trial to compare the outcomes of those who did with the ones who didn't. Scientific data regarding this theme will ever be composed of retrospective studies, weakening available evidence. Even for those who are to begin therapy, the choice of the right moment for treatment is not discussion free. The only published randomized controlled trial on this issue was not free of controversy [10].

Furthermore, in this context, the experience of living with a chronic, potentially mortal disease, is not yet accountable, in a sense that there isn't a target to aim for improvement, other than postponing the beginning of dialysis or death. Many decisions are often based on existing laboratory data and others, like blood pressure, which, although very important to drive medications, are seen by the patients as mere numbers. When a patient is informed that creatinine is rising, meaning that probably kidney failure is worsening, he often answers back that he feels well and has no limitations to his usual life, so he sees no need to worry. The disease is often asymptomatic until late stages. Meanwhile, organs and

systems are continuously worsening and becoming irreversibly damaged. The invoice will come later, in the form of morbidity and mortality. On the other hand, these numeric landmarks of disease are the gold standard references to clinical practice because clinical research has been guided by them [11].

1.2 Epistemological Pathway

The need to combine clinical data and the real life of the patient, lead us to set a search for other ways of measuring well-being and try to include its several dimensions in a broader framework that could allow a better evaluation and management of each patient, pursuing a better life, as far as health is concerned. As taking care of chronic patients is like managing a part of their health, the first idea that came to our mind was to make an analogy with management tools, namely the Balanced Scorecard (BSC), idealized by Kaplan and Norton in 1992 [12]. A BSC with clinical data would be perfect to guide the management of a patient with chronic disease.

The concept of BSC is very interesting: it is a management tool created to classify organizations, not only by their financial results, but also taking care of customer satisfaction, seeking excellence in the internal process and caring about learning and improving. It can be brought down from the organization perspective to a person one, in a process called cascading, allowing individual evaluation.

In the clinical setting, an analogy could be tried at this individual level. If we consider the global treatment of a patient as a major strategic goal, it can be categorised and structured into several aspects to which a physician must pay attention. As in the original Balanced Scorecard, a Clinical Balanced Scorecard (CBS) could be developed, also with four strategic dimensions, each one expressed by measurable endpoints:

- firstly, the core angle, represented by financial results of the management model would have its counterpart in the clinical and analytic results;
- secondly, costumers' satisfaction, which would correspond to the feedback given by the patients when they report their well-being and rehabilitation;

- thirdly, the pursuit of excellence of the internal process, that could be associated with concerns on doing things right (i.e. making decisions with a good cost-effectiveness ratio so the maximum number of patients could be treated with available resources);
- finally, the organizations' ability to investigate and develop could be translated to the teaching capacity of the physicians to patients, so that the patients can also participate in their own rehabilitation efforts, and the indicators would be the accomplishment of healthier lifestyle driven attitudes.

In the clinical setting, the "client" is the patient. From a deontological perspective, this should always be the priority. For this reason, this section of the BSC was chosen to be the first to be addressed within the scope of the present research work.

On the other hand, measuring outcomes reported by patients is becoming the gold standard of evaluating quality of care [13] and many tools are being developed and studied. Each one addresses a particular aspect of patients' lives. As far as we know, most of Patient Reported Outcome Measures (PROM) are studying patients when they were already on dialysis or transplanted, but less work has been done with pre-dialysis patients [14]. There is increasing awareness for a new paradigm in the management of these patients: the upgrade from the survival point of view to an increased quality of life and the need for its accountability [15]. In this context, well-being is, thus, a fundamental concept for the research being reported.

The validation of a set of patient-related outcomes is of seminal value to the construction of a reliable Clinical Balanced Scorecard.

1.3 Motivation and Objectives

We face this work as a contribution to a better understanding of life with kidney disease. This exploratory work aimed at looking for a better measure of what is in stake, when it is time to decide to move to a new phase of the patients' lives, and contributing to

a more complete evaluation of a patient who is at the other side of the desk, waiting for medical decision or guidance. That measure must be based on well-being and decisions must be based on when and how dialysis can be supplemental to the continuous loss of well-being that the disease brings.

The way to the ideal patient-reported measure, demands a strong connection between patients' characteristics and important life events in their lives. It is, thus, of primary importance:

- to disclosure connections between patients' attributes (demographics, comorbidities, level of kidney function) and life events, such as beginning of dialysis, hospitalizations, usage of emergency services or death;
- to evaluate the representativeness of the available indicators, as far as this specific disease is concerned;
- to assess their predictive value, in relation to important life events, surrogates of illness.

Secondarily, as we are dealing with renal patients, it was also considered important to reach a better understanding of which is the best way to estimate kidney function on a well-being perspective.

Thirdly, given the importance and the impact that comorbidities have on outcomes, it is of central importance to understand what the best marker of those conditions is so that their influence can be best assessed.

Finally, among the several endpoints classically considered in literature (the ones that usually guide medical decisions, as well as research), we felt it would also be important to check which one(s) would be the patients' favourite(s), in line with the search of giving voice to the patients and hierarchize their expectation and contribute to a better life experience.

1.4 Structure of the Document

The present work is composed by six chapters, including this introduction:

In Chapter 2, *Chronic Kidney Disease*, a brief review about Chronic Kidney Disease is made, focused on methods to measure results and criteria to drive decisions. At the end of the chapter, the clinical indicators that currently drive medical decisions are highlighted.

Chapter 3, *Managing Chronic Disease and Measuring Quality of Care*, covers aspects of chronic diseases, how they have been addressed in terms of care organization and thoughts on how it can be accountable for continuous improvement, including a review of key performance indicators of healthcare, under diverse points of view.

Chapter 4, *Experimental Work*, describes the research done in search for indicators of performance, simultaneously reliable and easy to use on everyday life.

In Chapter 5, *Discussion*, results of experimental work are reviewed, looking for benchmark and trying to find clues to its validation.

Finally, Chapter 6, *Conclusions and Future Work* presents some conclusions about this work and envisages relevant topics that might be explored in the future.

2 Chronic Kidney Disease

2.1 What is Chronic Kidney Disease?

Chronic Kidney Disease (CKD), formerly called Chronic Renal Failure, is defined as the progressive and irreversible loss of kidney function for longer than three months, irrespective of the cause [16] [17]. It is due to structural or functional abnormalities that lead to a decreasing number of working nephrons, the functional units of the kidneys. Although the remaining nephrons, trying to compensate for the loss of renal mass, by dilation and hyperfiltration, ultimately, they become fibrotic and lose their function. This is a vicious cycle that ends up in a total loss of function which is incompatible with a normal life and ultimately requires Renal Replacement Therapy (RRT) by dialysis or kidney transplantation for survival [18].

Some discussion has taken place about the parameters and thresholds that could be considered as the limiting definitions of CKD. These came to be albuminuria above 30mg/day, Glomerular Filtration Rate (GFR) below 60 mL/min/1.73m^2 and the presence of anatomic abnormalities of kidneys and urinary tracts [19].

Recent trends have widened the definition of CKD, leading to the inclusion of patients, who, in spite of having normal renal function, present markers of kidney damage, such as abnormalities of blood or urine composition as well as abnormalities detected by imaging examinations. It ended up including people at increased risk of developing CKD who could benefit from an integrated effort to improve outcomes, although they may not yet have renal failure *stricto sensu*.

2.2 Clinical Guidelines

The Kidney Disease Outcomes Quality Initiative (KDOQI) was launched by the National Kidney Foundation (NKF) in 2002 [16]. It was the successor of an earlier set of guidelines published in 1997 (Dialysis Outcomes Quality Initiative - DOQI) specifically

directed at problems of dialysis patients [20]. The assumed goal of the 2002 KDOQI initiative was to broaden the scope of this task to all stages of kidney disease. Later, in 2012, the mission was renamed "Kidney Disease Improving Global Outcomes" (KDIGO) [21], after a sequence of updates.

These were two sets of guidelines that, among several others, were intended to increase global awareness of CKD and gather the available evidence of the best medical options to diagnosis, investigate and treat this disease. Three important results of these initiatives have been the new name for the disease (CKD), a new classification and the settlement of a new conceptual model for the natural history of CKD.

The first important result of this initiative was the change of the name of the disease. The concept CKD replaced the old designation of this condition (Renal Failure), which is now reserved for the most advanced stages of the disease, when GFR decreases significantly. The concept of End-Stage Renal Disease (ESRD) is now left for those patients who are on RRT (dialysis or transplantation). Moreover, Terminal Renal Failure was definitively abandoned, enhancing the new paradigm of a chronic, rather than a terminal disease. And an interesting aspect about this shift of name is related to the replacement of the word "renal", of Latin origin, by the word "kidney", of Anglo-Saxon root. It must be noted that this decision was taken in the USA context, in order to increase the general American population awareness of this problem.

A remarkable achievement of this initiative was the establishment of a grading system. The aim of this system was to guide stratification of risk for complications and progression of CKD, as well as to guide the disease management. Furthermore, this grading system has been very useful to help decisions on treatments and define prognosis, intensity of monitoring and patient education (Table 1).

Table 1 - CKD Stages [16]

CKD Stage	eGFR (mL/min)	Description
1	> 90	Kidney damage with normal or increased GFR
2	60 – 89	Kidney damage with mild decrease in GFR
3	30 – 59	Moderate decrease in GFR
4	15 – 29	Severe decrease in GFR
5	< 15 or dialysis	Kidney failure

Also, KDOQI presented a new conceptual model that represents a continuum of development, progression and complications of CKD, each phase requiring a different approach and management (Figure 1). Complications of CKD are diverse and include consequences of impaired clearance of toxins, of cardiovascular disease, of albuminuria, of deficient regulation of the internal milieu, of deficient production of hormones and of drug accumulation [22].

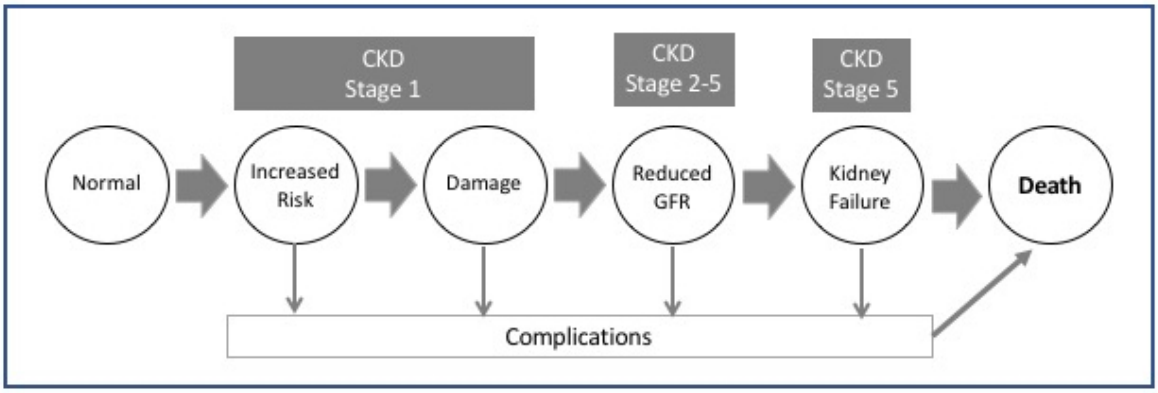


Figure 1 - Conceptual model for CKD (adapted from [16 22])

In the original 2002 KDOQI, estimated Glomerular Filtration Rate (eGFR) was the only variable considered for stratification. The upgrade of the KDIGO framework brought a new discriminator in Stage 3, which was divided into two sub-categories, designated 3a (eGFR between 45 and 59 mL/min) and 3b (eGFR between 30 and 44 mL/min). Albuminuria was also included as a prognostic marker. The reason for albumin staging addition was the independent risk for death and morbidity events that albuminuria has shown to be [23].

Albuminuria has become a marker, not only of kidney damage, but also of overall cardiovascular risk.

Figure 2 shows the KDIGO prognostic framework. The conjunction of the values of GFR and albuminuria gives an estimated risk for all-cause mortality, cardiovascular mortality, ESRD, CKD progression and Acute Kidney Injury (AKI). These were expressed in the original model within the context of a traffic light staging system. Four colours were defined, representing the increasing likelihood of developing future kidney and cardiovascular complications (green, yellow, orange and red). Although this staging system was useful to determine which patients need more intense monitoring, more therapy management tools are needed for risk prediction at the individual level.

Risk of morbidity and mortality, according to GFR and albuminuria level				Persistent albuminuria categories (units in mg of albuminuria / g of creatinuria)		
				Normal to mildly increased	Moderately increased	Severely increased
				< 30 mg/g	30 - 300 mg/g	> 300 mg/g
GFR categories, description and range (units in mL/min, normalized to 1,73 m2 of body surface)	G1	Normal or high	>= 90	**Low**	**Moderate**	**High**
	G2	Mildly decreased	60 - 89	**Low**	**Moderate**	**High**
	G3a	Mild to moderately decreased	45 - 59	**Moderate**	**High**	**Very high**
	G3b	Moderately to severely decreased	30 - 44	**High**	**Very high**	**Very high**
	G4	Severely decreased	15 - 29	**Very high**	**Very high**	**Very high**
	G5	Kidney failure	< 15	**Very high**	**Very high**	**Very high**

Figure 2 - Prognosis of CKD by GFR and albuminuria category (adapted from [21])

2.3 Epidemiology

CKD is a public health problem with worldwide implications [24]. It is a major economic burden with significant costs in health care [25] [26]. RRT is very expensive and accounts for substantial costs to national health systems. In the USA, for example, in 2015, there were 703,243 patients on RRT, spending more than 33 billion USD of the Medicare budget.

However, in spite of outstanding technological evolution and developments, outcomes remain poor [27]. Simultaneously, many countries in the world do not have conditions to maintain a comprehensive program of chronic dialysis, and patients die without an opportunity to be treated [28].

The above-mentioned data refers to those patients who actually started RRT. However, CKD begins long before that moment and all epidemiological studies have the important problem of the non-existence of solid criteria to start measuring the progression of CKD. It is also true that most people with CKD are not aware of it, so this disease can be pictured as the classical image of an iceberg of which only the top (the most advanced cases) is seen, while most cases (the milder ones) are asymptomatic and, because of that, hidden [29]. Therefore, CKD is, thus, underdiagnosed and underreported, leading to a silent progression, often escaping health systems surveillance and preventive programmes. This fact also has obvious implications on outcomes.

The Third National Health and Nutrition Examination Survey (NHANES III) study [30] has reported a prevalence of CKD of 16.93% in the 2013-2014 cohort after several previous cohorts with prevalence between 13 and 15%, demonstrating that it is increasing. A worldwide estimation of the population in RRT reached a number larger than 3,600 million people [31]. Geographic and racial differences apply [32]. The growth of cardiovascular disease as well as diabetes and hypertension continuously lead to an increased incidence and prevalence of CKD [33-35].

According to the yearly report of the Portuguese Society of Nephrology [36], during the year of 2017, there were 2,372 new patients on RRT, corresponding to an incidence of 230 new cases p.m.p., and by the end of 2017 the prevalence of CKD patients on RRT was 1,965 cases p.m.p., corresponding to 20,259 patients, 12,741 of which were on dialysis (both peritoneal and haemodialysis), and 7,518 carried a kidney transplant. Although the incidence has stabilized in the last 10 years, Portugal still ranks as number 1 in Europe for prevalence and number 9 in the world for incidence of CKD and number 5 in prevalence, only behind Taiwan, Japan, USA and Singapore.

On the other hand, another source of controversy it the fact that some patients may just be ageing, not getting sicker, as it is also well known that GFR decreases with age [37 38].

2.4 Aetiology

The current main causes of CKD are diabetes and arterial hypertension [39]. Other important causes are Primary Glomerulonephritis, Adult Polycystic Autosomal Disease, urinary tract malformations, chronic pyelonephritis, obstructive tract disease, and systemic diseases of immunologic origin, like Systemic Lupus Erythematosus (SLE) or vasculitis. In addition, haematological malignancies, like multiple myeloma, and viral infections, as well as amyloidosis, can lead to CKD. Sometimes, pathological conditions that cause AKI episodes that don't recover, progress to CKD. Chronic diseases, like malignancies or hepatic viral infections, can also present as both AKI and CKD [40].

Nephrotoxins may also play a role in development of CKD. Drugs such as nonsteroidal anti-inflammatories, aminoglycosides and lithium are examples of medicines where continuous use increases the risk of CKD, and the list is long [41]. Finally, there are diseases that involve the kidney, at the genetic level [42], and by indirect mechanisms that can lead to kidney injury, for example, sickle cell anaemia [43]. Familial nephropathy is an ill-defined group of diseases that can also be in the origin of CKD. Components of this group tend to be identified with exploration of the human genome [44].

There is also a strong link between cardiac and kidney disease [45-50]. It was found that patients with cardiac disease and dyslipidaemia, particularly high Low-Density Lipoproteins (LDL) levels [51] are in greater risk for kidney disease. Concerning obesity [52] and smoking [53 54], although epidemiologically related [55], no direct cause-effect relationship has been found with CKD, suggesting that concomitant conditions are responsible for both risk factors and kidney disease. In many cases there is a "chicken and egg" situation, making it difficult to tell which came first.

Patterns of aetiologies of CKD have a significant geographic variability [56]. These conditions are dependent on racial/genetic differences but are also related to habits and lifestyle (with salt ingestion, smoking and cholesterol levels at the top), and socio-demographic factors.

Nevertheless, there is still an important number of patients that reach end-stage renal disease without knowledge of their condition and the cause of those patients' CKD is

still classified as unknown. This also depends on the nephrological coverage of a given region or country [57].

2.5 Physiopathology

CKD is a heterogeneous group of disorders characterized by modifications of kidney function and structure. It is the common final pathway of many diseases that injure the kidneys, both primarily and systemically. Partial loss of renal mass leads to adaptive physiological change. As nephron loss progresses, there is a combination of hypertrophy and hyperfunction of the remaining nephrons [18 58 59]. This is why body water and concentrations of sodium, potassium, calcium, phosphorus and uremic toxins, like urea and creatinine remain within the normal range in mild and moderate renal failure.

This adaptive hyperfiltration has a limit beyond which different symptoms may be observed, such as volume overload due to deficient water excretion or increased serum levels of toxins due to decreased urinary excretion, namely ammonia compounds, hyperuricaemia, hyperkalaemia or hyperphosphatemia, to mention the most common. There can also be anaemia and mineral bone disease due to lack of synthesis of hormones (Erythropoietin and 1,25-Dihidroxi-cholecalciferol, respectively). Arterial hypertension is a common finding of CKD and is due to a variety of mechanisms, both related to retention of water and salt, and to hyperactivity of the renin-angiotensin-aldosterone axis and processes of oxidative stress and insulin resistance [60].

Some of these homeostatic responses are responsible for abnormalities of laboratory test results or symptoms and signs that appear throughout the course of the disease and often constitute the main focus of physicians when they follow patients with this disease.

Metabolism of drugs can also be disturbed, due to several reasons: oedema can lead to altered volume of distribution and decreased gastrointestinal absorption. Protein binding may also be altered thus leading to reduced renal excretion and drug retention. There is often the need to either adapt the dosage of a drug or the interval between drug

administrations. All patients therefore with renal disease must be monitored closely, particularly for signs of unexpected drug toxicity [61].

2.6 Natural History

CKD is asymptomatic until late stages. Clinical manifestations are very heterogeneous and depend mostly on the underlying cause and severity of the disease. Symptoms that appear in more advanced stages are related to complications, such as volume overload, arterial hypertension, anaemia, hyperkalaemia, hypocalcaemia, hyperphosphatemia, hyperparathyroidism, susceptibility to infections, increased risk to cardiovascular disease, decreased physical capacity, cognitive impairment and increased drug toxicity.

These complications can be due to accumulation of toxins or drugs, can be direct consequences of albuminuria or cardiovascular disease, of a deficient regulation of the internal milieu or can be caused by deficient production of hormones. Some of these complications, if not controlled, can be a cause of death.

The full picture (so-called “uremic syndrome”) may include asthenia, anorexia, nausea, vomiting, weight loss, pericarditis, peripheral neuropathy, volume overload, hyperkalaemia, metabolic acidosis, hypertension, anaemia, bone disease and central nervous system abnormalities, including headache, sleeping disorders or cognitive changes, ranging from loss of concentration to seizures and coma. This constellation of symptoms appears irregularly over the course of the disease. It is variable from patient to patient and its intensity may prompt the patient to seek urgent therapy advice. Many times, this has a correlation with the speed of progression and presentation of the disease and with comorbidities, rather than the grade of kidney dysfunction.

2.7 Diagnosis

Either by the classical definition and according to KDOQI and KDIGO definitions, the decreased GFR must be persistent over the last three months so that the diagnosis of CKD can be considered. It is fundamental to check clinical files in search for past measurements such as creatinine, urine dipstick, urinalysis and sediment examinations. In addition, imaging exams and especially ultrasonography may show small kidneys with reduction of cortical thickness. Demonstration of the progression of renal function over time is also mandatory, since one single measurement is not enough to classify the patient as having CKD. Ruling out AKI is of paramount importance, as the strategy to each one of these groups of patients is completely different.

It is also important to identify the cause of CKD, if possible, because it allows specific therapies, when available, to be directed at preventing further progression and injury. The rate of progression, risk of complications and possibility of transplantation are not the same for all CKD causes. Unfortunately, very often there is no specific therapy to the underlying disease that is causing kidney injury, and in those cases kidney protective measures are all we have to offer to the patient, aiming at delaying disease progression.

2.8 The Difficulties of Measuring Kidney Function

Although kidney function usually denotes the blood purification processes, kidneys have several other important tasks. Beyond clearing toxins from the blood, kidneys are fundamental players not only in the regulation on the internal milieu components, namely water, ions, pH, blood pressure, but also as endocrine glands that produce hormones such as erythropoietin, renin or activated vitamin D. All these factors can be the cause of impairments or complications, and many of them have been correlated to symptoms and signs of the clinical picture of uraemia [62].

The EUTox Work Group [63] is a working group of the European Society of Artificial Organs and an endorsed working group of the European Renal Association (ERA-EDTA) that

is committed to discovering new toxins and disclosing their importance. There are more than one hundred identified uremic toxins and many of them have no clinical importance. Therefore, it is not surprising that some aspects of kidney disease have not evolved in parallel with laboratory test abnormalities.

Some of the kidney functions are performed by the glomerulus, other by the renal tubules. There may be disease in both components of the nephron, but also in the renal vasculature [64] and interstitium [65 66]. Nevertheless, GFR has been considered to be the best index of the purification processes of the kidney and its decline is the gold standard measurement of kidney disease progression. As the disease is clinically silent until late stages, there has been a great deal of effort to find a marker which correlates between its blood concentration and the percentage of functioning kidney. The importance of measuring GFR transcends its use in the clinical setting. It serves as both predictor and outcome in the research environment and results of investigations are interpreted taking this into consideration. The need for a rigorous index of kidney function is unquestionable.

The molecule to explore as representative of GFR would be one that has three features: it is freely filtered by the glomeruli; it is neither secreted nor reabsorbed in renal tubules; it is not metabolized inside the kidney.

Several substances and techniques have been studied to meet these criteria [67 68]: inulin, cystatin, some radiographic contrast agents (for example, Iohexol or Iotalamate), radioactive isotopes (for example, 125-iodine marked-Iotalamate) and creatinine. Most are exogenous; they must be administered to the patient. Inulin is generally used in research and the laboratory context. Radioactive isotopes are used in nuclear imaging. Other techniques such as Magnetic Resonance Imaging have been tried in the research context [69]. Cystatin and creatinine are both used in the clinical context, the latter being more popular because there is more experience with it and it is less expensive. So, the choice has mostly focused on the measurement of serum creatinine [70].

The concept of "creatinine clearance" is defined as "the virtual volume of plasma that is cleared of its creatinine in each unit of time" [71], and it is used interchangeably with GFR. The usual operational unit is mL/min, although it can also be μmol/L, according to the International System of Units. Normal values depend, among others, on age, gender and

race, but they are often around 100 mL/min, which allows us to roughly associate the value to a percentage of normality.

The classic method to estimate creatinine clearance requires a 24-hour urine sample, however, this is difficult for the patient and introduces a potential source of error, as the collection of urine is often incomplete. Another cause for loss of accuracy in more advanced cases is the small quantity of tubular secretion of creatinine, whose percentage becomes significant when GFR is very low, changing the final result. Therefore, formulae have been developed to estimate GFR and, each one with its imperfections, has performed its task both in clinical and research settings (figure 3). [72]

Cockcroft-Gault formula [73]

$\frac{(140-\text{age})*\text{weight}}{72*\text{creatinine}}$ * 0.85 (if female)

MDRD formula (6 variables) [74]

170 * creatinine$^{-0.999}$ * age$^{-0,176}$ * 0,762 (if female) * 1,18 (if black) * urea^{-017} * albumin^{0,318}

MDRD formula (4 variables) [75]

175 x creatinine$^{-1.154}$ * age$^{-0.203}$ * 1.212 (if black) * 0.742 (if female)

CKD-EPI formula [76]

If female and creatinine < 0.7 mg/dL: $144 * \left(\frac{\text{Creatinine}}{0.7}\right)^{0.329} * 0.993^{\text{age}} * 1.159$ (if black)

If female and creatinine > 0.7 mg/dL: $144 * \left(\frac{\text{Creatinine}}{0.7}\right)^{1.209} * 0.993^{\text{age}} * 1.159$ (if black)

If male and creatinine < 0.9 mg/dL: $141 * \left(\frac{\text{Creatinine}}{0.9}\right)^{0.411} * 0.993^{\text{age}} * 1.159$ (if black)

If male and creatinine > 0.9 mg/dL: $141 * \left(\frac{\text{Creatinine}}{0.9}\right)^{1.209} * 0.993^{\text{age}} * 1.159$ (if black)

Figure 3 - Formulae used to estimate GFR

[Units: age (years); serum creatinine and urea (mg/dL); weight (Kg)]

The oldest and still most used formula to estimate GFR is the Cockcroft-Gault (CG) formula, first published in 1976, which uses serum creatinine values, age, weight and has a correction factor for gender [73]. It is not corrected for race, being very sensitive to variations

of muscle mass.

Another important formula is the Modification of Diet in Renal Disease Study (MDRD) equation [74]. This formula was first published in 1999 and has 6 variables: serum creatinine, urea and albumin, age, gender and race. Later, in 2006 [75], another formula was developed, using only four variables (creatinine, age, gender and race), demanding a standardized measurement of serum creatinine and claiming to provide reasonably accurate GFR estimates in patients with chronic kidney disease and a measured GFR of lower than 90 mL/min per 1.73 m^2. This 4-variable equation is increasingly being used, both in clinical and in research context. However, some claim that, in subjects with GFR over 60 mL/min/1.73 m^2, it may underestimate renal function [77], as well as in elderly and women [78].

Nevertheless, MDRD formulae were never universally accepted as the ones to be used routine and controversies still go on [79]. Furthermore, CG is the easiest to use. Hundreds of studies have been performed to address this controversy. A direct comparison is difficult because many studies don't use standardized measurements of creatinine [80]. That's why other approaches were tried. A reanalysis of NHANES database has led to the outset of the most recent formula, the CKD-EPI equation [76], which considers age, gender, race and clusters of creatinine values, separating lower and higher ones. In fact, this is not a single formula, but a combination of eight, and estimation of GFR through this set of equations has supposedly allowed estimation of CKD prevalence closer to what is thought to be the real value.

All of these formulae have the problem of not being validated for children or elderly, for whom special formulae were developed [81-83]. Some other formulae have been proposed. One of them is Lund-Malmo formula [84 85], which claims to be more accurate in the presence of established CKD, opposed to CKD-EPI formula which, according to these authors, would be preferable for screening tests. Another one is the Haematocrit Urea and Gender (HUGE) formula [86 87], which brings a different approach, being useful for diagnosis and prognosis of CKD. One other formulae is the Mayo Quadratic formula, which claims to address the measurement, not only of diseased people, but also healthy ones.[88]

In fact, the exact value of glomerular filtration rate is not the essential. The final use of these formulae is to frame the current kidney function of a particular patient in one of

the KDOQI framework's stages, previously mentioned. Moreover, these formulae are only useful in stable, "steady-state" patients. They are also not supposed to address, for example, hospitalized, febrile or catabolic patients, or the ones with AKI. They only give estimations of GFR.

An isolated estimation of GFR must not be analysed alone. It must always be interpreted in context with the patient's disease. An abnormal GFR value in an otherwise healthy person can be a false positive test and laboratory error should be considered. The same applies to a value which does not fit in the usual disease progressions of the patient.

Besides, creatinine, being a metabolic product of a muscular component (creatine), it is dependent on muscular mass, varying according to gender, race, weight and age. All these are potential factors of error, requiring standardization so that they can be safely used as surrogates of GFR [89]. The same happens with proteinuria, which only appears when lesions are already established and may not be present in early phases, when there could be opportunity for preventive intervention. Some argue that more important than an isolated measurement is the rate of decline of kidney function [90].

The association between AKI and CKD is also a matter of intense study, as there is increasing evidence that the former often leads to the latter. In this context there have been developments regarding biomarkers of kidney injury before kidney glomerular function begins to fall. Some of them have been correlated to the subsequent development of CKD. Among them are Neutrophil Gelatinase-Associated Lipocalin (NGAL), related to renal ischaemia or infection, Kidney Injury Molecule-1 (KIM-1), also detectable following ischaemic kidney injury, and Liver-type Fatty Acid Binding Protein (L-FABP) and Asymmetric dimethylarginine (ADMA), which have shown to be upregulated, as well as increased urine levels, in AKI and CKD, involving complex pathways of nitric oxide metabolism [67]. Also, in paediatrics, some of these biomarkers are being investigated and making their way to recognition [91]. Yet, there is still a long way to go until they become gold standards of kidney lesions of kidney functions in clinical context or research targets.

Meanwhile, we must rely on GFR as the main marker of kidney function, so that it can guide us to effective interventions that slow down or halt the progression of CKD. This is particularly a hard job because, although GFR declines very quickly on later stages of the

disease, it decreases slowly at the beginning, hampering the detection of evolution during that time, which is very long.

However, even in more advanced phases, in which creatinine clearance is already recognized as being indicative of how kidneys clear toxins, it is still just a number that often fails to link to the real capacities of the patients' lives with the fewer disabilities they can live with. It is very important to get a strong correlation between estimated GFR and life events, such as hospitalization or death, the milestones that really matter to patients.

2.9 Strategies for Management and Performance Indicators

Recommendations for specific therapies are beyond the scope of this text. However, as a summary, it may be said that there is a consensus for the five broad strategies that should be followed [92 93]:

a) treatment of reversible causes of renal failure

b) prevention or slowing kidney disease progression

c) prevention and treatment of the complications

d) adjustment of drug doses to the level of estimated GFR, when appropriate

e) adequate preparation of the patients in whom RRT will be required.

Table 2 lists some of the CKD complications that are usually addressed in patients with progressive CKD and the performance indicators used to address them. Some of them are still controversial because even if they are recognized to occur during disease progression, their overall impact on quality of life, morbidity and mortality is not known.

The usual approach to CKD management includes addressing each one of these problems [94]. Some of them have implications on others. Therefore, acting on one of these issues often leads to changes in others, both beneficial and deleterious. The usual office practice is to check each one of the various clinical parameters and prescribe medicines or give advice towards antagonizing the factors responsible for their cause.

Table 2 - Performance indicators for the clinical problems of CKD

Clinical problems to be addressed	Performance Indicators
Volume overload/oedema	Weight; Presence of Godet's sign; Pulmonary Sounds; turgor of jugular veins; hepatomegaly.
Losing weight (for obese patients)	BMI variation
Hyperkalaemia	Serum Potassium
Metabolic acidosis	Serum Bicarbonate; Serum CO_2
Arterial Hypertension	Arterial Pressure (systolic and diastolic)
Cardiac dysfunction	Echocardiogram data
Anaemia	Haemoglobin, Haematocrit
Iron kinetics	Ferritin, Transferrin Saturation, Hypochromic erythrocytes
Mineral Bone Disease	Serum Calcium and Phosphorus; Serum Intact Parathyroid hormone (PTH); Alkaline Phosphatase
Dyslipidaemia	Total Cholesterol; HDL and LDL Cholesterol; Triglycerides
Hyperuricemia	Serum Uric Acid
Sexual dysfunction	Yes/No: data from history
Malnutrition	Weight; Serum Albumin; Physical Examination
Inflammation	Leukocytes, C-reactive Protein *(and also pro-inflammatory cytokines: IL-6, IL-10, TNF-α, complement components, prostaglandins, leukotrienes, not currently used in clinical practice)*
Glycaemic control (*for diabetic patients)*	Glycated Haemoglobin
Thyroid dysfunction	Thyroid-stimulating hormone
Pericarditis	Echocardiogram; Cardiac Murmur on physical examination
Uremic neuropathy	Yes/No: data from history
Uremic Bleeding	Yes/No: data from history

General patient education	Performance Indicators
Salt restriction	Yes/No: data from history *(also: urinary sodium may be of use)*
Moderate protein restriction	Yes/No: data from history
Smoking cessation	Yes/No: data from history *(also: Serum Cotinine)*
Nephrotoxic drug eviction	Yes/No: data from history
Lifestyle modifications (diet, exercise, etc.)	Yes/No: data from history
Vaccination	Yes/No: data from history; specific serology

At the beginning of the follow-up, there is a time in which any physician can lead the treatment because goals are general, broadly related to cardiovascular prevention, there being no specific demands, as they are similar and sometimes concurrent with other diseases. Many times, specialists, other than nephrologists, also come across CKD while treating other organ diseases: family physicians, internists, cardiologists, endocrinologists, vascular surgeons or neurologists, to mention but a few. It is important to stress that up to a point, these general strategies are available to any physician.

Referral to a nephrologist generally depends on national and local practice habits, guidelines and protocols, and on the availability of medical services [95]. There is though one indication for a nephrologist appointment that meets a consensus: GFR below 30 mL/min [96]. This indication for referral to the nephrologist is based on treatment of specific complications that usually appear more often from this milestone on. This early referral, as opposed to later, has demonstrated to be associated with lower mortality after initiation of dialysis [97]. Another study [98] reinforces this idea and emphasizes that it is true irrespective of the aetiology of CKD and enhances the benefits of a very early" (more than 12 months) preparation for RRT.

Preparation for RRT is also an important reason to refer a CKD patient to a nephrologist. This includes choice of modality, construction of adequate vascular access or peritoneal catheter, vaccination, preparation for transplantation when appropriate, and specific treatment of complications such as anaemia, mineral bone disease and metabolic acidosis with drugs that, at least in Portugal, are only available at the nephrologist's office.

Currently the nephrologist doesn't work in isolation. Dealing with CKD implies being part of a broader framework that some have called Disease Management [99]. The continuous monitoring of the patient status and circumstances is mandatory for the success. Beyond clinical and physiological indicators, other key performance indicators must be followed for success. Among them are health promoting behaviours, well-being and quality of life, health care utilization and, because resources are not infinite, health care costs. These are, in general, the components of the proposed Clinical Balanced Scorecard that we are aiming for.

3 Managing Chronic Disease and Measuring Quality of Care

A chronic disease is a disease that lasts for a long time, very often a lifetime. It cannot be cured neither it just disappears. Although its symptoms are sometimes less severe than those of the acute phase of the disease, chronic disease demands permanent care and brings long lasting suffering to the patient. Chronic diseases may be progressive or can evolve by bursts, often resulting in incomplete recovery, in partial or complete disability and ultimately leading to death.

A survey published in 2014 [100] refers that 117 million Americans had at least one chronic condition and at least 25.5% of the people had at least two. Arterial hypertension, obesity, coronary heart disease, stroke, diabetes, cancer, arthritis, hepatitis, weak or failing kidneys, asthma, and Chronic Obstructive Pulmonary Disease (COPD) are among the top causes of death, 70% of which are chronic conditions [101]. Two of these chronic diseases (heart disease and cancer) together account for nearly 46% of all deaths. Arthritis is the most common cause of disability. In Europe numbers are not significantly different [102].

A detailed definition of Chronic Disease is beyond the scope of this text, as all definitions available agree that Chronic Kidney Disease (CKD) fulfils criteria for being considered chronic [103].

3.1 The Individual Level

The primary need of a patient when he seeks the physician with some kind of complaint may not necessarily be the cure. Although this may be absolutely true for acute diseases, it may not be so when we deal with incurable diseases, which become long lasting. In these cases, the patients will only aim to live as long as possible with the best possible quality of life: that is translated into less suffering, less disease burden, less consumption of medical care and the most complete rehabilitation they can get. In other words, the chronic patient aims to maintain his autonomy and self-helping skills, his communication capabilities and his social interaction. In the evidence-based medicine era, the scientific community is

looking for the standard of care that can best pursuit that goal. This is what should be considered Quality of Care. This where the concept of disease management arises, meaning a broader sense than simply "treating" the diseased person.

The classical approach to chronic disease has been mechanistic, hospital and physician-centric, considering that the cause has either an anatomical or a chemical foundation. Following this paradigm, the physician addresses each one of the potential clinical problems of a given pathologic condition and how they express, both clinical and analytically, and the main focus of attention is given to those symptoms, signs and very often (too often) laboratory tests as outcomes. The problem is that all of them, especially the latter, have little impact on patients' perception of improvement. When these diseases don't bring progressive disability, they are silent until late stages, when clinical untoward events, some of them catastrophic, happen. In fact, laboratory tests are just numbers that often mean nothing to patients' everyday life. Not rarely, the toll that they have to face to keep some lab test within the right limits is greater that the perceived benefit against degradation of health status and, therefore they don't comply with the physician's recommendations.

Furthermore, there is a selection bias. Depending on when vigilance starts, time to hard endpoints that really impact people's life (for example, a catastrophic event like hospitalization or death) is not uniform, making it difficult to explain the need of a treatment or a change of lifestyle. Every patient knows another one with the same disease, for whom the result of a medical decision has been different. The same happens with endpoints in research context: rather than considering a defined number to demonstrate a given intervention, it might be proposed an interval between two stages as the standard measure for progression, both upwards or downwards (improvement or worsening) of a certain medical condition. Another problem is that patients have multiple comorbidities and it is also important to analyse the mutual interference of all variables.

This calls for a dynamic view of the problem. The concept of disease trajectory is, thus, most appropriate in this context, as it reflects the evolution and, by that way, reproduces the way the patient (and his support) is coping with the disease. The difficulty is to find a variable that can easily express that progression. There is a need to evaluate concepts like well-being, quality of life, depression, rehabilitation, functionality,

comorbidity, happiness, and many others. These should, in fact, be the goals to pursue [104]. This is why we have chosen the designation "Management of Chronic Patient", to include a broader dimension than simply "Treatment of the diseased person", as usually used currently.

3.2 The Organizational Level

Chronic diseases represent a heavy burden, not only to the patient, but also to his family and the society, both considering personal suffering and economic issues. The growing aging of populations in modern societies led to an increase of the number of chronic patients, and no country is truly prepared for that. The problem is not new: in 1996, 75% of health expenditure was on chronic care [105]. Since then it didn't improve: according to US Center for Disease Control and Prevention (CDC), that number rose to 86% in 2010 [106], 48% of the people having at least one chronic pathologic condition. This is important, not only due to direct medical costs, such as medication and increased utilization of health services, but also to indirect ones, as for example, decreased work productivity and premature retirement.

At a governmental level, chronic diseases tend to be seen as being, neither urgent, nor the eventual improvements easy to advertise, falling in politicians' priorities rankings, as compared to competing calls for budgetary attention. However, it has become evident that the traditional model of acute care, based on episodic contacts between the patient and health institutions is no longer capable of meeting the long-term needs of an aging, chronic diseased population.

Consequently, there have been important efforts to deal with this problem. Ambulatory care is increasingly becoming recognized as the right way to do it, where preventive actions are the core activity and, because of that, they are potentially more effective since they are monitored more closely to families' and people's lives. Even when patients need differentiated care, some new solutions are being designed, such as home-hospitalization [107] [108] and palliative end-of-life care [109].

So far, several models of care created to deal with chronic disease have been proposed, mostly in the US, and their detailed discussion is made elsewhere [110]. As a summary, it can be said that all of them are multidisciplinary, involving nurses, social workers, psychologists and other health care professionals. This is why single-standing private practice medical offices are no longer adequate to deal with these conditions. In general, it can be said that the ideal environment to treat chronic diseases is a health delivery system or health organization, as long as they promote a proactive, patient centred, evidence-based delivery of care, patient safety, as well as community linkage and health education programmes for patients and families to promote self-management as far as possible. Some claim that each system should be directed to one type of disease, to homogenize beneficiaries and increase efficiency, but this is not consensual, because many patients have multiple conditions and separation of care of several pathologies makes more difficult to integrate problems of each patient [102]. Another essential requisite is the existence of a good omniscient information system where everything is recorded for future memory and as a part of a learning structure [111].

An expert panel meeting on older adults with multiple chronic conditions, held by the National Institute on Aging in 2012 [112] recommended that any organized program of care of older persons with multiple chronic conditions should always complete a brief initial composite measure including symptom burden, measures of depression and anxiety, information on daily activities, assessment of physical and cognitive functions and evaluation of caregiver burden. These are broadly the components of Patients Reported Outcome Measures (PROM) generally used in this context, which are going to be addressed further on.

A shared essential aspect to all is the need to be accountable, trying to find the right outcomes, as one cannot improve what can't be measured. Performance indicators are endless, each one directed to a detail that can be addressed, ranging from global to individual issues. The search for such quality outcome indicators is clearly a priority.

3.3 The Importance of Assessing the Success of Healthcare Interventions

Success, in general, is understood as making progress towards strategic goals or periodically achieving some level considered to be adequate or desirable. In clinical context, this notion is often intangible, because it is subjective and context dependent. In some cases, it is very difficult to define clearly what the main purpose of medical action is, as far as clinical outcomes are concerned. Nevertheless, regardless of the situation, one can summarize success of medical care as "delivering value to the patient" [113]. This delivered value can be translated in a life with quality, free from limitations due to health problems.

In acute diseases, these definitions are clearer: the patients want to be cured of the disease they are suffering from and they long to return to their previous healthy state as soon as possible. In this context, being sick or healthy are two mutually exclusive conditions in which a person can be.

In chronic conditions, as already said, patients are going to face their disease for a long period of time (if not forever) and patients and their families want to live as long as possible, with the less possible distress. This can be expressed by different outcomes. For example, patients may want to return to work especially if the disease made them stop working. In addition, they will want to recover from the disease where possible or when a flare has occurred. Most importantly, they look to regain independence, if some of it was lost and to avoid a bad outcome, such as a myocardial infarction, stroke or dialysis.

Measuring quality of care is, thus, essential. It will allow: quality assessment of the care itself, after creation of standards for comparison; interpretation of epidemiological data so that it can have relevant impact on future decisions; validation of clinical trials results and endorsement to practice guidelines; cost-effectiveness analysis, encouragement of patients for compliance; other scientific and economic purposes, namely payment for performance and continuous improvement.

3.4 The Point of View of Quality Management

Donabedian, back in 1966 [114] in his seminal paper, outlined the main aspects of the evaluation of quality of care. This opened doors to new ways of facing this issue. He pointed out that evaluation of the medical activity, as the result of patient-physician interaction, was dependant on three interdependent vectors: structure, process and results.

The first one, structure, is related to the settings in which the process takes place. It refers to adequacy of facilities, equipment, administrative support, number and qualifications of professionals, existence of information and institutional issues. In a sense, baseline characteristics of a sample of patients being intervened can also be considered a structural feature of the system, because they are the departure point and have impact on outcomes.

Process is the second dimension of quality and it is related to appropriateness, completeness and redundancy of the interaction of the patient with the health professional or institution: medical history, physical examination, accurate diagnostic tests or preventive management.

Finally, there is a criterion that more accurately estimates quality than the measurement or verification of pre-requisites of structure and process. According to Donabedian [114], it's the measurement of outcomes (results) that can best lead to a degree of quality evaluation which can be reflected in good results to the patient, contextualized with the other two criteria (structure and process). In common language efficacy and efficiency are designations often used. The first tells how a goal is being or has been achieved, the second relates it to the consumption of resources.

A good method to improve quality is to periodically check outcomes and evaluate the influence of process and structure on them and how changes in the latter can improve the former. This is the classical "plan-do-check-act" cycle, or Kaizen, which is the gold standard of quality improvement programmes [115 116].

3.5 Health-Related Quality of Life

The definition of Health formulated in 1948 by the World Health Organization (WHO) Constitution [117] ("Health is a state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity") has evolved to a multidimensional level, including physical function, emotional and cognitive functions. This also includes perceptions about present and future health, morbidity, premature mortality and life expectancy, as well as various symptoms and physiologic states [118]. This goes along with concerns regarding the coping with the disability in chronic diseases. Even when a chronic disease is reasonably controlled, it is the way it is experienced by the patient that endorses the success of medical decisions.

Morbidity is, therefore, the relevant concept in this context. The need for hospitalization or usage of medical services are indirect markers of well-being and, therefore, of Health-Related Quality of Life (HRQoL). These measures give information about the lowest levels of health but give little information about smaller disabilities. Pursuing improvements in these indicators will provide only a minimal assessment of patient improvement. If, however, differences between perfect health and smaller disabilities were measured and improvement was pursued, the level of health enhancement would be greater.

This apparent disparity of concurrent concepts has led to the search of a composite index of overall health by combining data about the presence or absence of various diseases and conditions. Quality of life (QoL) is a comprehensive popular term that encompasses the sense of well-being, and includes aspects of happiness and satisfaction with life as a whole. Being subjective, it may have a different meaning for each person in a given society and is necessarily different across cultures and geographies. It is a balance of several dimensions, both positive and negative: physical performance, vitality, social inclusion, religious beliefs, education, employment, life satisfaction, wealth, family issues, finance and environment.

Another definition of QoL, is "good quality of human life" [119]. It has several dimensions, ranging from the individual up to the society level. These lead to diverging focuses and very different definitions. On the community level, these dimensions together

build the complete picture of a society's well-being: ecology, economics, politics, education, safety, security, health, are some of the areas of interest. Many of them are related to cultural issues and expectations. Nonetheless, QoL is always recognized and presented as a target to achieve.

In this process, the WHO proposed a definition of individual QoL: "the individual's perception of his position in life and in relation to his goals, expectations, standards and concerns" [120].

An important determinant of individual QoL is health. Without health, a person can't enjoy life to the fullest. In other words, his/her QoL becomes diminished. The WHO addressed this matter, by creating instruments to measure HRQoL [120]. HRQoL has been defined as the "impact of disease and treatment across the physical, psychological, social and somatic domains of functioning and well-being" [121]. Consequently, every disease or condition can be assessed by the impact it has on QoL and many attempts have been made with this goal in mind. Moreover, the importance of the health component of QoL is justified because it is a very important variable in one's life. Measuring HRQoL gives a standardized idea of the patients' experience of the disease and its toll in several dimensions on human life.

According to some authors, given this subjective feature, QoL is not being correctly measured, as it can only be suitably measured by determining the opinions of patients and by using validated instruments [122] [123].

3.6 The Point of View of Utility

Quality Adjusted Life Year (QALY) is a measure of estimated quality of life. It was developed as a measure of effectiveness and utility for decision-making in several contexts, mostly managerial, budgetary and resource assigning. The basic concept is that individuals move through health states over time and that each health state has a value attached to it. Any situation of a disease or disability would represent a lower value, taking into account a

discount of an amount of time correspondent to the imparity brought about by that relative inability [124].

There is a derived concept, the Disability Adjusted Life Years (DALY) that intends to measure the impact of health loss by the quality of life. On the contrary, QALY considers both quality and quantity of living, considering health gain. The difference between them is rather technical and its explanation is outside the scope of this text [125].

Both are methods of evaluation of the impact of health interventions as a result of a resource allocation. They assume that a year of life in perfect health is worth 1.0 QALY and death corresponds to 0.0 QALY. It combines duration of life with a level of utility of a given intervention, and the utility is the improvement of health brought by a given treatment or decision. Variation of utility and survival are then compared to help steer medical and political decisions. For example, a 3-year survival after a surgery with a utility improvement of 0.7 corresponds to 2.1 QALY; another competing treatment that brings a 9-year survival with utility of 0.4 corresponds to 3.6 QALY. The latter would be the favoured measure for medical decisions or budget assignment.

Utility is calculated by asking the patient about their options regarding their valuation of health benefits of a given decision in a pertinent time frame. Value is measured in terms of preference between two options. An earlier benefit is valued over a later one, like when applying a discount interest rate to the value foreseen. If a group is considered, benefits across the individuals are considered and used for the group.

Another technique to compute utility is the Time Trade-off (TTO). TTO is used to measure the QoL that a person or group is experiencing. An individual would be presented with the following question: "*Imagine that you have 10 years left to live. You have two options: either live those 10 years in your current health status or give up some of those years in exchange for the rest of the time in perfect health.*" [126] [127]. The answer given by the individuals show how many years in the current health state they would be willing to trade-off, in order to regain full health. This answer can be used to calculate the individuals' quality of life in the present health state. If a person answers, for example, three years, it means that he/she compares seven years of perfect health with 10 years in the current status

assigning the same value to both situations. His/her TTO value is 0.7. This result is often used to compute QALYs, combining mortality and morbidity in the same scale.

An important limitation of this kind of measures is the subjectivity that they carry, both to the evaluation and to the perception of urgency by each person. Moreover, as its calculation is very complex, it is of limited use in the clinical setting [128].

Therefore, this concept is mostly used for cost-effectiveness analyses, rather than the follow-up of individual cases. It is the most important unit used by National Institute of Clinical Excellence (NICE), in the UK, to assess cost-effectiveness of new treatments [129]. Nevertheless, necessary data for its calculation comes from sets of patients and is influenced by their everyday life. In a way, it can be considered, at least, a worth-mentioning PROM-derived index and it may be useful in ecological studies.

3.7 Surrogate Outcomes

In chronic care, a specific endpoint (good or bad) is often inappropriate to use because it is too far in time or too catastrophic to be useful for a model of continuous improvement that uses the "plan-do-check-act" cycle [115].

Therefore, mortality, probably the most used endpoints in research, has relevance only if we are dealing with a life-threatening disease within the span of the observation period. Chronic diseases often have a long period before mortality occurs, lessening the significance of this endpoint in a short-term analysis. In these cases, it is more relevant to know how patients are coping with such a disease and how it is preventing them leading normal lives or to check if they can still work and earn, or to count hospital admissions or visits to the physician or the emergency department, and aim for their reduction, than to wait for their deaths. Time to an event can also, in this context, be an intermediate endpoint of interest, especially if it refers to a relevant endpoint to achieve or avoid.

These are the so-called surrogate endpoints that are frequently used as replacements of clinical endpoints, as research guides or to adjust decisions and processes.

Going back to the Donabedian's framework [115], it corresponds to adding an intermediate outcome between the process and the final outcome.

It is important that these intermediate outcomes have three qualities: firstly, that they are relevant to patients, showing improvement of their disease status, rehabilitation, quality of life improvement, the reduction of adverse events or avoidable suffering; secondly that there is a rationale between the disease process and the measured outcome; thirdly that physicians' actions have some impact on those endpoints, so that they may be correlated to the improvement of the specific indicator.

In other words, the link between the surrogate endpoint and the clinically relevant outcome must be validated, either with a logical explanation by aetiopathogenic or pathophysiologic mechanisms or by a proven causal epidemiological link. There must be the possibility of predicting the effect of the intervention, such as a pharmacologic or non-pharmacologic treatment, on the clinical outcome. There should also be as fewer confounding factors as possible.

These surrogate endpoints should also be indicative of what the impact of the disease is on patients' lives. Good examples of this are: absences from work, visits or referrals to the emergency department; hospital admissions and number of inpatient days (this correlates with severity of complications, but it is also dependent on organization of hospitals, together with the medical action itself). Sometimes it may be necessary to build composite endpoints, gathering occurrences of similar meaning, to assure that they happen in a frequency big enough to allow statistical analysis [130].

3.8 Comorbidity Indices

Comorbidity is defined as the presence of more than one distinct disease in the same individual [131]. It is widely recognized as an important contributor to outcomes both because it has impact on morbidity and also because it introduces bias in selection in the research context. In 1987, Charlson created the first tool [132] aimed at prospectively attempting to reach a method for classifying comorbid conditions which might change the risk of mortality

for use in longitudinal studies. An important drive for this research was the finding that many trials excluded patients with comorbidities to prevent their interference in the results, but this led to sample analyses that were less representative of clinical reality, decreasing reproducibility of results. The original Charlson comorbidity scale included 17 conditions, each one scored according to the risk of mortality.

Later on, in 2011 [133], a work of revalidation took place, adapting the scale to newer realities in an international context. This update followed the recognition that some diseases that formerly were considered to be life limiting could have improved prognoses. Components of both scales are presented in table 3.

Table 3 - Charlson Comorbidity Indices (1987 and 2011 versions)

Comorbidities	Original 1987 scale [132]	2011 update [133]
Myocardial Infarct	1 point	-
Congestive Heart Failure	1 point	2 points
Peripheral Vascular Disease	1 point	-
Cerebrovascular Disease	1 point	-
Dementia	1 point	2 points
Chronic Pulmonary Disease	1 point	1 point
Connective Tissue Disorders	1 point	1 point
Ulcer disease	1 point	-
Mild Liver Disease	1 point	2 points
Diabetes	1 point	-
Hemiplegia	2 points	2 points
Paraplegia	-	2 points
Moderate or severe renal disease	2 points	1 point
Diabetes with end-organ damage	2 points	1 point
Any tumour	2 points	2 points
Leukaemia	2 points	2 points
Lymphoma	2 points	2 points
Any solid tumour	6 points	6 points
Moderate or severe liver disease	3 points	4 points
AIDS	6 points	4 points
Age (each decade above 40)	1 point	
Highest Score (most diseased)	**35 points (plus points due to age)**	**34 points**

The Charlson comorbidity index has been widely accepted as a standard for evaluation of comorbidities, both at clinical and research level. A search of PubMed with keywords such as "Charlson" or "Charlson Comorbidity Index" returned more than 10,000 references, from all specialities, ranging from clinical to managerial subject areas. It has been very important to allow patients with comorbidities to participate in clinical trials and widen the span of its results. It is interesting to verify that most articles still use the original version even though it has been challenged as outdated.

Another comorbidity scale was published in 2002 by Davies [134], specially directed to CKD patients on peritoneal dialysis. It is a very simple score that considers seven conditions: malignancy, ischaemic heart disease, peripheral vascular disease, left ventricular dysfunction, diabetes mellitus, auto-immune disease and any other significant disease. It also adds points according to age and number of comorbidities. The gradation ranges from zero to two points and it correlates to mortality risk. A comparison with the original (1987) Charlson comorbidity index [135], found that both Davies and Charlson comorbidity scores were significant predictors of outcomes, with the Charlson Comorbidity Index being a stronger predictor for mortality and the Davies score a stronger predictor of hospitalizations.

Three other scales have been presented as alternatives to quantify the impact of comorbidities: one is the Index of Coexistent Diseases (ICED), another is the Disease Burden Morbidity Assessment (DBMA) and the third is the Sickness Impact Profile (SIP).

The first one, ICED, is a questionnaire that aggregates the presence and severity of 19 medical conditions and 11 physical impairments, gathering data into two scales (one related to disease severity, the other showing physical impairment). In the nephrological context, this was used in the Haemodialysis (HEMO) study [136 137]. It has also been used in orthopaedic context [138]. It. A problem with this test is its size, which means it is impractical to use in a clinical daily context.

The other comorbidity index, DBMA, was originally published in 2005 [139]. It is an extensive questionnaire that covers 21 health conditions, not only asking for their existence, but also inquiring about the disability that each one of them causes to the individual. Compared to others, it can be easily completed, including older people, without the limitation of having to be administered by professionals with medical background. This is,

usually a limitation to using these instruments in large samples of patients either in primary care settings or the general population.

Finally, SIP, which was originally published in 1975 [140], more than a comorbidity index, is a generic health status measure of change in behaviour as a consequence of HRQoL. It claims to be a measure of sickness related to dysfunction based on activities of daily living. It has a 136-item questionnaire divided in 12 categories: sleep and rest, work, eating, home management, recreation and hobbies, ambulation, mobility, body care and movement, social interaction, alertness behaviour, emotional behaviour, and communication. There is a shorter version with 68 questions [141 142]. Both versions are very long, are difficult to use in the clinical setting and as a result are not being widely used.

3.9 Patient Reported Outcome Measures

Treating chronic patients with success depends on a strong bond between the physician and the patient. The former is supposed to look for a complete understanding of most dimensions of their patients' experience of the disease. Not only are symptom status and physical functions important, but also mental health, social function and general well-being are relevant issues to be perceived by someone who has the responsibility to prescribe drugs, give important advice that changes patients' lives, and perform invasive techniques. All these interventions must be programmed and executed with the exact needs of the patients in mind and look to solve their health needs. No one can assess those needs better than the patients themselves.

Rehabilitation, well-being and HRQoL are only some of the examples of important goals of medical treatment with subjective implications which are completely dependent on how the patient feels and complains, and on many characteristics of his personality, familial environment or social status.

PROM are tests that intend to get a standardized answer from the patients as a reply to questions or statements which represent several themes of interest and whose codification leads to knowledge of their opinions, feelings, experiences, capabilities and

perceptions. There are hundreds of PROM scales, which include health status assessments, functional status, symptoms and symptom burden reporting measures, health behaviours, experience with care, treatment satisfaction measures, economic impact measures, and instruments for assessing specific dimensions of the patient experience such as physical and mental performance, depression and anxiety [13].

It is also important to mention that, for most environments, in this acronym, patient refers, not only to the diseased person, but also to all related people of the micro-system around him/her: family, formal and informal caregivers and any related person. However, some institutions and authorities confine this designation to information that comes directly from the patient about the status of their health condition without an interpretation or amendment of his answer by a physician. The FDA has specific guidance for use on Medical Product Development to Support Labelling Claims [143], in which the definition demands the absence of an intermediate between the patient and the recorded data.

There is a similar concept that includes all patient care experiences, values, preferences, satisfaction, expectations and this is designated the Patient Reported Experience Measures (PREM). It is also used to assess quality of health systems, beyond individual patient status. In some contexts, PROM and PREM can be linked [144].

Limitations of PROM include aspects related to populations, namely very young, elderly and most fragile ones, low literacy, language and other problems of communication, culture and functional inabilities, both physical and cognitive. Cultural barriers also constitute a hurdle to overpass.

PROM can help decisions in several fields: in the clinical environment, to help diagnosis, stage diseases or monitor results of treatments; in research, it can be used as outcomes for testing medicines, devices or techniques; in management, to assess performance or serve as quality indicators of benchmarking; in society, to give information to patients in order to help choices of providers.

The proliferation of PROM has led to questions of validity. The National Quality Forum addressed this issue creating a framework for validation of the newly created PROM [145]. According to it, it is mandatory to document the conceptual and measurement model, the reliability (through internal consistency and reproducibility), the validity (content,

construct and criteria and responsiveness validity), the facility of the interpretation of scores, the feasibility the alternative modes and methods of administration, cultural and language adaptations and the capability of electronic health records.

Moreover, since 2004 a National Institute of Health (NIH) funded initiative named Patient Reported Outcome Measures Information System (PROMIS©) [146] [147] has also been trying to summarize many aspects of patients' information that only they can provide. The publicly expressed goal of PROMIS is to develop a "psychometrically validated, dynamic system to measure these patient-reported outcomes efficiently in study participants with a wide range of chronic diseases and demographic characteristics." [148]

Using a computer adaptive test with simple questions, it provides an instant report of health status reaching several different domains and returning results that may be compared to the general public and to people who belong to the same age and gender. Data has been being collected in a central databank and has led to the creation of hundreds of scales which intend to comprehensively score these subjective dimensions of the patient status. PROMIS© claims to be "a set of person-centred measures that evaluates and monitors physical, mental, and social health in adults and children. It can be used with the general population and with individuals living with chronic conditions" [149].

Some PROM are generic, others are disease targeted. Many of them address each one of these aspects and some try to handle them all. Generic tests are validated for the general population and aim at representing non-specific aspects of being ill. They are, in general, less sensitive to certain features of each disease. Their advantage is the ability to compare a more heterogeneous group of patients. On the other hand, disease-targeted questionnaires were validated for a particular condition, they are normally very specific, avoid ceiling or floor effect and intend to portrait the behaviour of a defined disease.

Figure 4 presents the global framework of PROMIS©.

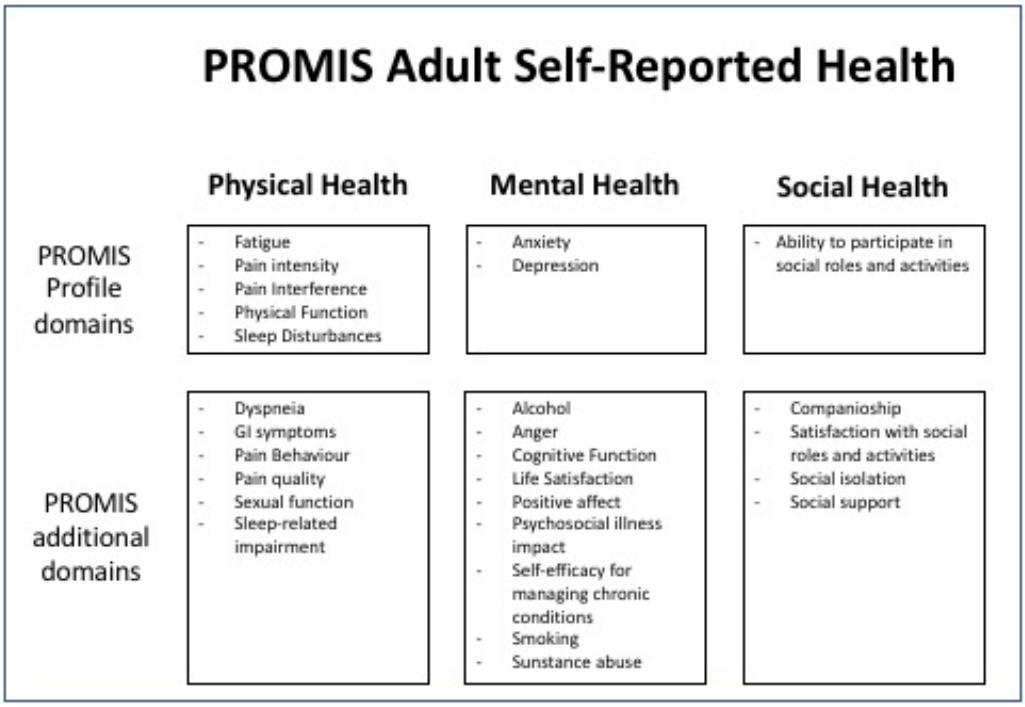


Figure 4 - PROMIS© Adult Self-Reported Health framework (adapted from [149])

In a broader sense, several kinds of information can originate a PROM: HRQoL; activity limitations (disability); symptoms and burden of disease; experience with care; health behaviours; QoL and patient satisfaction. Its scope can range from disease into other domains of patients' lives (Figure 5).

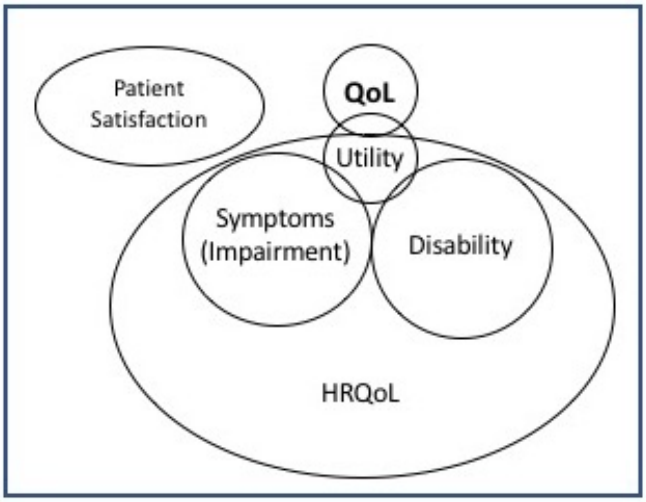


Figure 5 - Scope of PROM (adapted from [144])

Another issue is the cumulative difficulty and statistical noise by increasing the comprehensiveness of a given scale. On the other side of the spectrum are the simpler scales which induce loss of precision and information. The more we want to extract from a scale, the more complex the process of its validation becomes.

Table 4 summarizes some generic tools.

Table 4 - Selected generic PROM and domains they measure

Acronym	Full Name	Domains covered
MOS SF-36 [150] (*also, SF-20, SF-12, SF-6D*)	Medical Outcomes Study Short Form	Bodily pain, physical functioning, vitality, mental health, social functioning, role limitations due to emotional or physical problems, general health perception
QWB-SA [151]	Quality of Well Being – Scale Assessment	Depression
SIP [141]	Sickness Impact Profile	Physical composite, psychosocial composite, general health.
PROMIS-57 [146] (*also, 43 and 29*)	Patient-Reported Outcome Measurement Information System	Pain, physical function, fatigue, sleep disturbance, anxiety, depression, ability to participate in social roles.
WHOQOL-BREF [152]	World Health Organization Quality of Life Scale	Physical health, psychological, social relationships, environment
IIRS [153]	Illness Intrusiveness Rating Scale	Physical well-being, diet, work, finance, marital, sexual, family relationships, social relations and other aspects of life
PHQ [154]	Patient Health Questionnaire	Depression
SDI [155]	Social Difficulties Inventory	Everyday living, social distress, self and other money subjects
GAD-7 [156]	Generalized Anxiety Disorder 7-item Scale	Anxiety
ESASr [157]	Edmonton Symptom Assessment System revised	Pain, tiredness, drowsiness, nausea, appetite shortness of breath, anxiety, depression, well-being
ESS [158]	Epworth Sleepiness Scale	Insomnia
CH-RLSq [159]	Cambridge-Hopkins diagnostic questionnaire for Restless Leg Syndrome	Restless leg syndrome
HUI2 [160]	Health Utility Index	Pain, mobility, self-care, sensation fertility, emotion, cognition
EQ-5D [161 162]	Euro-Qol 5 dimensions	Pain, mobility, self-care, anxiety, depression, general health
LASA [163]	Linear Analog Self-Assessment Scale	Physical, emotional and social dimensions, summarizing 29 areas

Table 5 describes a CKD-specific PROM. Most of them have been studied in CKD patients already on dialysis or transplanted.

Table 5 - CKD disease-targeted PROM and domains they measure

Acronym	Full Name	Domains covered
QLI-D [164]	Quality of Life Index – Dialysis	Health and functioning, psychosocial/spiritual, social, economic, family, general health
KDQOL-LF, KDQOL-SF [165]	Kidney Disease Quality of Life (Long Form and Short Form)	Physical functioning, role physical, pain, general health, social function, emotional well-being, role emotional, energy/vitality
KDQ [166]	Kidney Disease Questionnaire	Physical symptoms, fatigue, depression, relationship with others, frustration
KTQ [167]	Kidney Transplant Questionnaire	Physical symptoms, fatigue, uncertainty, appearance, emotional
RQOLP [168]	Renal Quality of Life Profile	Physical activity, impact of treatment, eating and drinking, psychosocial activities, leisure time
CHEQ [169]	CHOICE Health Experience Questionnaire	Physical functioning, sexual functioning, sleep, diet, vitality, body image, bodily pain, cognitive functioning, mental health, social functioning, role emotional, role physical, work, recreation, travel, finances, dialysis access, freedom, general QoL
RDI-QLQ [170]	Renal Dependent Individualized Quality of Life Questionnaire	Physical functioning, sex life, enjoyment of food, restriction of fluid, physical appearance, family life, worries about the future, motivation, spiritual/religious, social life, friendships, work, leisure, activities dependency, freedom, social, prejudice

3.10 Objective Performance Status versus Perceived Performance Scales

PROM can provide data on the patients as seen from themselves or they can give an exact picture of how they perform certain tasks. They are not exactly the same thing, although both dimensions are important because each one shows one side of the coin. Each person stands at a level of Maslow pyramid at a given moment and that relative position also determines his vision and influences his expectations [171].

In fact, these objective indicators have different meanings to different people. The same level of performance in two persons is not perceived as equal by each one of them, and thus, the success of a given intervention is not recognized in the same way. In this case, although the objective threshold is achieved, medical care may not be recognized as useful.

During the course of a chronic disease, there must be a definition and undertaking of an unbiased treatment goal. Good examples of measures are the performance of the patient in relation to his daily activities: can he feed, dress and wash himself? Can he walk alone? Is he able to live independently? How much can he walk or run? Can he create and enjoy the more or less sophisticated pleasures of life? How is his social life? How much time does he spend of medical care? How many daily medications does he take to remain in equilibrium?

Thus, both in the research and clinical environments, as well as in managerial context, the most objective measures should be looked for so that results can be comparable. On the other hand, It has been demonstrated that performance and self-report measures may complement each other in providing useful information about functional status [172].

The ideal scale should be strong enough to support adequate medical decisions by reducing subjectivity and increasing objectivity, namely to be able to distinguish impairment due to dysfunction related to the studied disease or condition, or due to normal aging, and being able to eliminate bias caused by misplaced expectations.

3.11 Some Examples of PROM Scales

The medical speciality that makes the most use of these kind of scales is, by far, oncology. The reason is easy to understand: cancer is becoming a chronic, rather than a rapidly lethal disease and metrics are needed to assess prognosis and evolution, as well as providing indication and support to decision making when escalating those expensive and burdensome therapies. Another reason is that oncology is a leading speciality in pharmaceutical investigation [173] and these scales are very useful as instruments of research.

Gerontology, as well, is increasing its use: elder people get sick of many diseases that become chronic, emphasizing the need for measures of status that summarize all the effects of competing diseases. Moreover, dealing with proximity of death increases the relative

importance of indicators of success or failure, as far as health care is related, other than the prolongation of life itself.

Also, primary care is increasingly using PROM to help medical decisions and monitor patient valued outcomes. Recently, PROM based guidance showed improved health outcomes and fitted moderately with goals, specifically pain improvement, and opened ways for routine use of PROM as outcome measurements [174]. In this context, attempts for the development of a generic PROM questionnaire for primary care have been tested [175].

In the nephrology field, PROM scales are also being used, both in research and in the clinical environment, at the decision rather than at office level. A report of the PROM Measurement Group, at Oxford University, addressed this question with a focus on kidney disease [176]. A total of 29 different tests were reviewed and divided in four broad categories: generic measures, health utility measures, renal specific multidimensional questionnaires and symptom-focused questionnaires. Some were considered overlapping, other complementary. The report recommends that PROM should have a greater role in the National Health Service (NHS), namely through a combination of these tests.

In fact, the NHS has already implemented the National PROM programme whose intention is to monitor the effect of NHS interventions on QoL and well-being. The first programmes have been carried out with patients undergoing orthopaedic surgical procedures [177].

3.11.1 Karnofsky Performance Scale

Although Karnofsky Performance scale (KPS) is not a PROM in *strictu senso*, as data is obtained from external observation, rather than from the patients' own reports or answers, it is mentioned in this section because it uses data directly extracted from their daily lives, considering their performance, behaviours and activities.

KPS is a performance status scale that assesses the patients' actual level of function and capability of self-care, classifying them by their functional impairment. It summarizes their ability to perform daily activities, and the level of assistance that is required to do so. It was first described in 1949, in an article originally published as a chapter of a proceedings

book of an oncology symposium [178], establishing a gradation of 11 levels of autonomy, ranging from a complete autonomy to a dying status. This classification would help to evaluate the usefulness of using aggressive chemotherapeutic agents in the control or cure of neoplastic disease.

Since then it has been used thousands of times, as a numerical guide to patients' general health, in many environments, both clinical and in research, in a wide range of situations, from evaluation of patients to decision for therapy escalation, determination of appropriateness for nursing homes referral, stratification of patient samples, the evaluation of individual patients' response to treatment, alone or together with other objective measures. It is, by far, the most used PROM, in several areas of medicine.

The Eastern Cooperative Oncology Group (ECOG), working since the sixties, created a new scale [179], derived from the first, but is much simpler. It considers five levels: normal activity; symptomatic but nearly fully ambulatory; bed time less than 50%; bed time more than 50%; and unable to get out of bed. There was a good agreement between the ECOG and KPS with no statistical difference being found between them [180]. Later, in 2005, an Australian group tried to adapt it to a palliative care environment [181].

Despite the widespread usage of KPS, most of the research used to understand and systematize it was done in the eighties [182]. KPS is often used as a surrogate of dependence in activities of daily living (ADL) and an algorithm conciliating KPS and ECOG scales addressed this subject [182]: a KPS of 70 corresponds to ADL independence and a KPS of lower than 50 is equivalent to full ADL dependency.

In a longitudinal cohort study with stage 5 CKD patients managed conservatively it was found that functional status remained stable during the last year of life but declined steeply in the last months and weeks of life [183]. This concept of trajectory of disease is very important because disease is a dynamic process and it is essential to know the prognosis for a better treatment of these patients [184].

Table 6 presents KPS and ECOG scales in parallel, showing the equivalences between both.

Table 6 - Karnofsky Performance Scale and ECOG scale in parallel

Karnofsky Performance Scale			ECOG Scale
Interpretation	Score	Description	
Able to carry on normal activity and to work; no special care needed.	100	Normal, no complaints; no evidence of disease.	0 — Fully active, able to carry on all pre-disease performance without restriction.
	90	Able to carry on normal activity; minor signs or symptoms of disease.	1 — Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work.
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.	80	Normal activity with effort; some signs or symptoms of disease.	
	70	Cares for self; unable to carry on normal activity or to do active work.	2 — Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours.
	60	Requires occasional assistance but is able to care for most of his personal needs.	
Unable to care for self; requires equivalent of institutional of hospital care; disease may be progressing rapidly.	50	Requires considerable assistance and frequent medical care.	3 — Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours.
	40	Disabled; requires special care and assistance.	
	30	Severely disabled; hospital admission is indicated although death not imminent.	4 — Completely disabled; cannot carry on any selfcare; totally confined to bed or chair.
	20	Very sick; hospital admission necessary; active supportive treatment necessary.	
	10	Moribund; fatal processes progressing rapidly.	
	0	Dead	5 – Dead

3.11.2 Short Form 36 and Kidney Disease Quality of Life

The Medical Outcomes Study (MOS) was a health survey designed to investigate if variations in patient outcomes were explained by differences of care or specialty, as well as to develop practical tools for the routine monitoring of patient outcomes in medical practice [185]. Following that study, one of the tests that emerged as a marker of overall health status was the MOS Short Form 36 (SF-36) [150 186]. This initially had questions covering 40 health related concepts. Of these, eight areas were selected in a search for a generic standard instrument that would be easier to use and would add useful information to a more complete understanding of results. The final format of the questionnaire contains questions to provide measures in eight domains of HRQoL: physical function; role limitations due to physical health or emotional problems; bodily pain; energy/vitality; social interaction; mental health; and general health perceptions. The scale was constructed for self-administration by persons 14 years of age and older, and for administration by a trained interviewer in person or by telephone [186]. There are thousands of publications in many areas of medicine and many languages and cultural adaptations, namely in Portuguese [187 188].

The shift to the use of SF-36 in the nephrological context began in an attempt to validate this tool for end-stage renal patients [165 189] and the evolution of this scale came to be the most widely used one in the nephrological context, the Kidney Disease Quality of Life (KDQoL) test. This is a tool that includes generic questions plus some related to the burden of kidney disease. This part presents specific questions aimed at kidney disease symptoms. It allows an understanding of both physical and mental dimensions of the disease, expressed in eight domains:

- Physical Function;
- Physical Performance (“Role Physical”);
- Pain,
- General Health Status (“General Health”);
- Emotional Well-Being (“Mental Health”);
- Emotional Performance (“Role Emotional”);
- Vitality/Energy;

- Quality of Social Interaction ("Social Function").

These eight domains are often grouped in two synthetic variables, the Physical Summary, including the first four, and the Mental Summary, gathering the last four. One last question covers the patients' perception of change in health status. A whole summary score is not advised because it is not validated and also because it would lose the ability to discriminate between the several dimensions of HRQoL which supposedly would be the targets to follow for improvement.

KDQoL has become the preferred measure of HRQoL for CKD patients on dialysis. The test correlates with number of hospitalizations and mortalities in patients on chronic dialysis [190] [191], and with number of medications being taken (pill burden) [192]. There are also publications comparing therapeutic options [193], and the study of anaemia in CKD is the most studied subject as far as HRQoL is concerned [194]. Unfortunately, most studies were made in patients already experiencing renal replacement therapy (RRT) i.e. haemodialysis, peritoneal dialysis, as well as transplanted patients. Little is known about CKD patients prior to receiving RRT [195] [196]. A study on pre-dialysis CKD patients has shown significant differences between two groups of patients, one "well nourished" and another "mal nourished" [197].

There is another HRQoL test (EuroQoL-5D), which is often used, due to its simplicity. It covers 5 dimensions of QoL: pain; mobility; self-care; anxiety; depression; and general health. It was created by a European working group with the intention of complementing other quality-of-life measures and to facilitate the collection of a common data set for reference purposes [161] [162]. It is also validated in Portuguese [198].

3.11.3 World Health Organization Disability Assessment Schedule

The World Health Organization Disability Assessment Schedule (WHODAS) is an instrument for the generic assessment of health and disability. It was developed by the WHO, making it globally relevant and adaptable to all cultures and environments. Rather than being directed to any particular disease, it is intended to be used across all diseases, both physical and mental. It is the operationalization of the International Classification of

Functioning, Disability and Health [199]. The framework adopted by the WHO for measuring health and disability is set to be used both at the clinical office and epidemiological settings. It covers six domains of functioning: cognition (understanding and communicating); mobility (moving and getting around); self-care (attending to one's hygiene, dressing, eating and staying alone); inter-personal relationship (getting along, interacting with other people); daily life activities (domestic responsibilities, leisure, work and school); and participation in community activities (joining in community activities, participating in society) [200]. One of its objectives was to develop a simple, short and easy to administer health assessment tool. The result is expressed in standardized levels of disability. It has three versions, ranging from the most detailed 36-item, that takes about 20 minutes to complete, to the 12-item, lasting five minutes. It can be administered by an interviewer (both personal and computer assisted), a proxy or by the subject himself. The current release is 2.0 [201]. The Portuguese version validation was published in 2015 [202].

There are two ways to compute the scores of the WHODAS 2.0. The simpler short version assigns points to each of the answers i.e. from one point for "none" to 4 points for "extreme". At the end, all these points are summed up without any other operation, assuming an equal range of each category that can be answered. This simpler way can be best used in a clinical context. The most complex method, according to information provided by the WHO [203], takes into account different weights and severity. First it sums up the scores within each domain, then it sums all six domains and finally converts summary scores into a percentage. It is a reverse scale: the maximum score (100%) would correspond to the full disability.

A recent paper compared WHODAS 2.0 with another index of disability, the Modified Barthel Index. It concluded that the Modified Barthel Index doesn't consider the patients' perspective, although it could predict length of stay in a cohort of patients admitted into inpatient rehabilitation units after elective hip or knee arthroplasty, opposite to WHODAS which did. It suggests that both scales could be used as complementary in order to provide integration of clinical information with a PROM [204].

Another interesting paper found out that WHODAS 2.0 was associated with disabilities of upper and lower extremities HRQoL and suggested that WHODAS 2.0, as it

isn't targeted to a specific disease, it can be used to compare different diseases, as far as disability is concerned [205]. To our knowledge, WHODAS has never been used in CKD patients.

3.11.4 Short Physical Performance Battery

The Short Physical Performance Battery is a simple standardized test designed to assess physical performance and disability [172], after the Timed Up & Go test, previously used in nursing homes with elderly people [206]. It covers three areas: muscle strength (also called "sit-to-stand" performance), standing balance and walking speed. Most of the work done with this scale has been used in a physical rehabilitation context, not only in clinical [207], but also in a research context as an endpoint [208], or to assess patient compliance with allocated treatments in clinical trials [209].

It consists of three tests of lower-extremity function: assessment of balance by standing in three different positions, chair stand and walking (gait) speed, by walking four meters. Each of these challenges is scored on a scale from zero to four. The total ranges from zero (the worst performer) to 12 (the best performer). It has been shown that dialysis patients have worse scores than the ones with heart failure, COPD or a group classified as high cardiovascular risk [210]. These patients were selected from sample of dialysis patients but, as only candidates to kidney transplant were selected, it is indicative of how worse a general population of dialysis patients may perform. It has shown to have a correlation with QoL, measured by EuroQoL-5D [211], as well as disability, decline in health, increased hospital length of stay and death [212]. It was also used in elderly hospitalized CKD patients being predictive of incapacity and death in elderly patients after hospital discharge from an acute episode. It also correlated with CKD stage [213].

3.11.5 Satisfaction With Life Scale

Satisfaction with life is a subjective concept that includes several dimensions. It is the result of the interaction of physical, mental and social components. In addition, it includes the capacity of coping with adversities, resilience, disease resistance and capacity of

recovery, among others. At the individual level, it has been correlated with decreased risk of disease, illness, and injury, better immune functioning, better coping and faster recovery, more success at work, higher incomes, more fulfilling relationships, greater contribution to communities and longer life expectancy. At a nationwide level, it correlated with more political engagement and stability, lower divorce rates, more equality, and better records of civil liberty [214].

The attempt to quantify life satisfaction as a whole, led to the creation of Satisfaction With Life Scale (SWLS) in 1985 [215]. The scale does not assess satisfaction with life domains such as health or finances but allows subjects to integrate and weight these domains the way they choose.

It is an easy test to answer. Participants say how they classify five sentences in a 7-point scale, ranging from strong disagreement to strong agreement. These points are summed up and give a result that measures cognitive judgement of one's satisfaction to life. Overall the result amplitude ranges from five to 35 points, rating satisfaction with life in six grades.

Given the fact that satisfaction with one's life is dependent not only on physical and mental conditions, but also on personal expectations, it is interesting to note that the five sentences that compose this test cover broad themes of what one's life may be: it has questions about ideals; life conditions; success in achieving what is important in life; being satisfied with life; and regrets with past options. It intends to give a global assessment of a person's QoL according to his/her own criteria [216]. The authors argue that it is a suitable summary measure of well-being as it can adapt to the quality of life relative to one's priorities, being eligible as a single common metric of overall life satisfaction.

Moreover, there is a feature that authors value most in this concept: satisfaction with life is a cognitive/judgmental aspect of well-being, rather than with emotions. It is a global assessment of a person's QoL according to his own chosen criteria which are based on a comparison that the person sets for one's self, rather than externally imposed or judged important by the researcher. The subjectivity of the concept submitted is one's circumstances and hence valuable by itself. If it influences other outcomes, it will become a valid surrogate endpoint to pursue.

Therefore, SWLS is one of the most extensively used and validated instruments in well-being research. However, to our knowledge, it has never been published in CKD patients.

3.12 State of Progress and Rising Questions

Gathering all variables that compose the circumstance of a chronic patient, one can postulate a chain of events and conditions that may be faced as targets for medical attention. All of them can be addressed as far as CKD is concerned. Current guidelines are mainly focused in reducing the risk of cardiovascular morbidity and mortality, and in treating complications. They enhance risk factors which are targetable by pharmacological or technological device treatments. The drive for this priority is often a commercial one, as not every patient dies of cardiovascular disease and there is certainly something to be achieved, even for those who ultimately do. There must be other possibilities.

Therefore, physicians' interventions are generally guided by clinical and analytical variables that reflect changes believed to be in the origin of the disease but, although related, often fail to focus on a better life experience of the patient while waiting for the final event, as all chronic diseases will eventually lead to death.

Some intermediate important concepts arise at this stage, including Disability, QoL and satisfaction with life. Most studies on this area were carried out in dialysis or transplanted patients, where the control of statistic technicalities is easier. However, the relationship between these different concepts has never been studied in CKD patients before reaching the point when they need RRT.

This work aims to investigate these intermediate goals of treatment, with the view to replace the current ones as the targets to tackle when physicians treat and follow-up patients with CKD. They could serve as KPIs of the experience of being sick with this disease.

Kidney function measurement and comorbidity valuation from a well-being perspective were also two concerns during this research work.

Additionally, it was also an objective to find out what the preferences of the patients are, as far as medical care is concerned, and use them as the outcomes to follow, in order to approach a definition of success of a therapeutic treatment or strategy.

Meanwhile it is necessary to establish the relationship between these concepts (Disability, Quality of Life and Satisfaction with Life) and "hard" outcomes (beginning of dialysis, hospital admissions, visits to emergency room, worsening of lab results and death), with special emphasis on the ones that patients will consider priorities.

Some initial question areas came to our attention. These evolved into the research questions:

- Which eGFR formula is more useful at predicting of outcomes and correlating with well-being?
- How does a population of CKD perform as far as PROM are concerned?
- What are the most important predictors of PROM in a CKD population?
- How can PROM predict future endpoints?
- What are patients' priorities concerning their treatment? What are their preferences regarding what their physicians first concerns should be?

If an answer to these questions is found, the comprehensive tool for managing the chronic patient will be better understood and the path to its discovery will have begun.

4 Experimental Work

4.1 General Plan of the Work and Research Questions

The choice for reliable measures of well-being should be meaningful for the patients' demands. In addition, they should be related to the baseline characteristics of the patients they are supposed to be representing. It should also be mandatory that they can predict future endpoints, so that they can come to be used routinely in the clinical context. This experimental work intends to test published well-being tools to check if they fulfil those conditions. Chronic Kidney Disease (CKD) is a good model of chronic disease because it goes through different phases across a patient's life and it has several stages, each one with its ups and downs, but providing a suitable model for analysing targets of accountability and intervention for improvement.

This chapter addresses 5 topics, each one attempting to answer an investigation question:

1. After description of the methodology used for work *(section 4.2.)*, we present a baseline characterization of a Chronic Kidney Disease (CKD) Population in an outpatient clinic of a hospital of the Portuguese National Health Service: e.g. demographic data, comorbidity indices, kidney function and last year's events, such as hospitalizations and usage of emergency services. This section is mainly descriptive but it is important to the contextualization of the results to follow in other sections. *(section 4.3.)*
2. Regarding kidney function measurement, the question being asked was which estimated Glomerular Filtration Rate (eGFR) formula was more useful at predicting outcomes and correlating with well-being? Available evidence has been focused on finding what is the best formula to assess creatinine clearance, as representative of GFR. The focus of this research was to correlate the results with outcomes and markers of well-being. *(section 4.4.)*
3. How do PROM represent a CKD population? How does a CKD population perform as far as Patient Reported Outcome Measures (PROM) are concerned? As a

chronic disease, some impairments of life may have an impact of how patients describe their experience. We wanted to evaluate the performance of the sample of patients under review, and compare the results with other chronic diseases and with other series of CKD patients. In addition, it was important to look for baseline variables that could predict PROM scores. Among them, as literature presents two indices of comorbidities, it was important to evaluate which one was better in predicting both PROM scores and the defined endpoints. *(sections 4.5. and 4.6.)*

4. What is the impact of baseline variables on future endpoints? And how can PROM predict the defined endpoints at 24 months (mortality, beginning of dialysis, hospitalizations and utilization of emergency services? Achieving a good or avoiding a bad outcome is a goal of health care. A given PROM will only be useful if, beyond describing the well-being of the patient, and representing the context and conditions of patients, it is capable of predicting future outcomes known to be significant for the individual patient. This section we are looking for the PROM that fulfil these conditions. *(section 4.7.)*
5. What are patients' priorities concerning their treatment? What are their preferences regarding what their physicians' first concerns should be? Generally, some standard endpoints are assumed to represent patient and disease management goals. We asked patients for their opinion concerning these issues. We took six endpoints commonly described in the literature as the ones to follow to create scientific evidence for medical decisions and research (death, dialysis, hospitalization, emergency services usage, worsening of general health, and worsening of laboratory tests) and asked CKD patients for their opinion about what their physician's priority should be. *(section 4.8.)*

The integration of this information may allow the confirmation of our proposed conceptual model of relationships between baseline variables (demographic data, comorbidities, kidney function and previous year's events), PROM and defined endpoints (Figure 6).

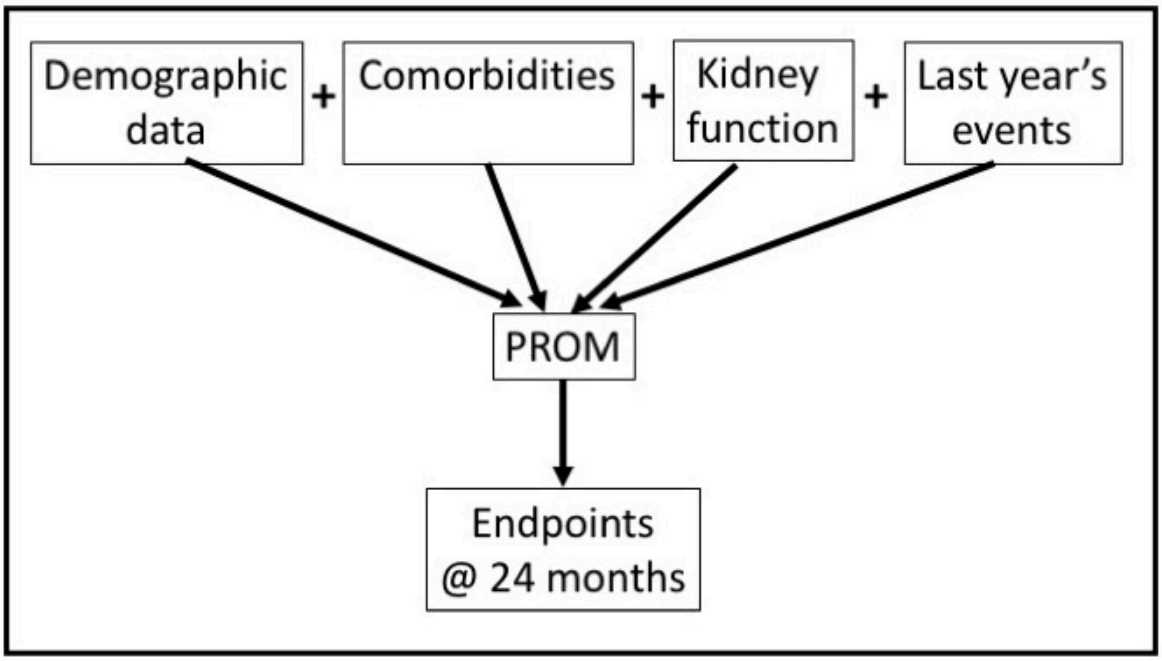


Figure 6 - Conceptual model/general plan of the investigation

Disclosing the influence of both baseline variables and PROM on "hard" endpoints at 24 months will lead to the identification of the ideal PROM, this will transfer the influence of the first ones on the latter. PROM fulfilling these two conditions of being both representative of baseline characteristics and predictive of the same endpoints as those baseline variables will be suitable for daily usage in the clinical context. They can then be considered as surrogates for those endpoints and the collection of the necessary data to compute that PROM should earn the right to be claimed as part of the medical appointment.

As demographic data, we have considered gender, age, employment situation, schooling and income. For comorbidities, we have chosen the Charlson Comorbidities Indices, both the original (1987) and the 2011 revised version. Regarding estimation of GFR, we have checked the performance of the four most published formulae (CG, MDRD 4, MDRD 6 and CKD-EPI). Finally, the last year's events recorded were hospitalizations and episodes of emergency room utilization.

As examples of PROM, we have selected Short Physical Performance Battery (SPPB), the World Health Organization Disability Assessment Schedule version 2.0 (WHODAS), the

Satisfaction With Life Scale (SWLS) and the Kidney Disease Quality of Life version 1.3 (KDQoL).

Finally, as "hard" endpoints we chose Death, Beginning of Dialysis within 24 months, Hospitalization and Emergency episodes during 24 months.

4.2 Patients and Methods

4.2.1 Preparation of Work, Regulatory and Legal Issues

In compliance with applicable legislation and guidelines [217], authorizations from local Ethics Committee, hospital's Administration Board and National Commission for Data Protection (CNPD) were obtained prior to all study-related activities.

All patients accepting to participate signed an Informed Consent form before all study-related activities. During all stages of the work, patients were anonymised and identified by a study number (ID01-ID60), making impossible to identify individuals.

Copies of these documents are presented in the appendix.

4.2.2 Recruitment, Deliverance of Questionnaires and Collection of Medical Data

We recruited 60 patients from an adult outpatient clinic of Nephrology in a public hospital of the Portuguese National Health Service, on the day of a regular visit to the nephrologist, in 19 different days, from December 2014 to April 2015.

At the end of a normal medical appointment, they were invited to participate in this study, the goal of the investigation being orally explained by the author. The criteria of inclusion were having the diagnosis of CKD and being able to understand the questions. After the Informed Consent was signed, the patients were introduced to the assistants who delivered the questionnaires in an adjacent room, without the presence of the author.

To ensure uniformity of deliverance, two trained university designated assistants delivered all the questionnaires. All interviews were conducted in Portuguese. Each interview was performed in private and lasted between 30 and 40 minutes. Some older

patients, who asked for it, were allowed to have a family member or informal caregiver in the room, but attention was made neither to let them answer, nor to let them help to perform the tasks. There was no payment or other benefit for patients and their families, and no change of the regular treatment was made to the participating patients.

Clinical data from the patients was extracted from the digital files of the hospital (Software "SClínico Hospitalar®", Portuguese Ministry of Health). For some older data, paper files were also consulted.

4.2.3 Demographics, Comorbidities, Estimated Glomerular Filtration Rate and Medical Events in the 12 Months Before Baseline

Demographic data collected was: gender, date of birth (to compute age), formal education ("schooling"), family income and employment situation (active/retired). Categories studied were:

- For age, three categories were considered: below 65, between 65 and 75 and above 75 years old.
- For schooling, 4 groups were considered: less than primary education, completed primary education, completed secondary education and university degree.
- For income, 3 levels of annual revenue were considered: below 7,000€ (National Minimum Wage), between 7,000 and 20,000€ and above 20,000€.
- For employment situation, 2 conditions were considered: active and retired.

Coexisting comorbid conditions were assessed by the Charlson Comorbidities Index scales, both 1987 [132] and 2011 [133] versions. Data was extracted from patient files by a unique independent physician, to ensure uniformity.

Four formulas were used to compute the estimated Glomerular Filtration Rate (eGFR), which was used as an evaluation of kidney function, in order to classify patients according the CKD stages. The formulas were: Cockcroft-Gault (CG) [73], MDRD with 6 variables (MDRD6) [74], MDRD with 4 variables (MDRD4) [75] and Chronic Kidney Disease

Epidemiology Collaboration (CKD-EPI) [76]. This calculation was made at three time points: baseline, at 12 months and at 24 months after answering the questionnaires. Data was inserted manually in an Excel spreadsheet and results were recorded in mL/min.

Retrospective data was also collected, regarding number of hospital admissions, inpatient days, episodes of ER, time since last hospital discharge and time since last episode of ER in the previous 12 months before baseline.

4.2.4 Instruments Used to Evaluate Patient Reported Outcome Measures

Among the many available questionnaires, four were chosen to represent several dimensions of personal well-being on the patient point of view: WHODAS 2.0 (Portuguese version with 12-items) for assessment of disability [202], SPPB for physical performance [172], SWLS for general satisfaction with life [215] and the generic part of KDQoL (Portuguese version 1.3) [187] , for Health Related Quality of Life (HRQoL). The first three were chosen because of their simplicity and ease of use, being good candidates for utilization at the bedside, and the last one because it is more widely accepted and already validated for kidney disease patients.

The short version of WHODAS 2.0 explains 81% of the variance of the long version questionnaire [200]. We used the simple scoring system, which is more practical to use in a hand-score approach and may come to be chosen as the method of choice in the busy clinical context with pencil-paper interview situations, the setting used for the collection of data. As the WHO website [218] says, “the simple sum of the scores of the items across all domains constitutes a statistic that is sufficient to describe the degree of functional limitations”.

SPPB and SWLS were used in its standard form, so that it could be applicable for clinical use in a medical office environment, should it fulfil the demanded conditions.

Regarding KDQoL-SF, eight HRQoL domains were discriminated: Physical Functioning (KDQoL_PF), Role Physical (KDQoL_RP), Pain (KDQoL_Pain), General Health (KDQoL_GH), Vitality/Energy/Fatigue (KDQoL_VT), Social Function (KDQoL_SF), Role Emotional

(KDQoL_RE), and Emotional Well-Being/Mental Health (KDQoL_MH). These variables are shown in table 7.

Table 7 - KDQoL evaluation tool (adapted from [165])

Variable name	Dimension name	Questions related	Number of questions
KDQoL_PF	Physical Function	3a, 3b, 3c, 3d, 3e, 3f, 3g, 3h, 3i, 3j	10
KDQoL _RP	Role Physical	4a, 4b, 4c, 4d	4
KDQoL _Pain	Pain	7, 8	2
KDQoL _GH	General Health	1, 11a, 11b, 11c, 11d	5
KDQoL _VT	Vitality/Energy/Fatigue	9a, 9e, 9g, 9i	4
KDQoL _SF	Social Function	6, 10	2
KDQoL _RE	Role Emotional	5a, 5b, 5c	3
KDQoL _MH	Mental Health	9b, 9c, 9d, 9f, 9h	5

There are Physical and Mental Health summary scores, plus the burden of kidney disease score. However, these as well as a total score have not been validated against predictors or outcomes and as it would be unclear as to what they would represent, their inclusion is not recommended [219]. Therefore, we didn't use them and, in the scope of this work, each of the domains is meant to be analysed separately as a variable with its intrinsic meaning.

In relation to the other 43 questions of KDQoL-Long Form questionnaire, about symptoms/problems of kidney disease and effects of kidney disease, they are intended to evaluate specific CKD symptoms that may be present in the late phases of the disease, just when they are about to reach the need for dialysis. In early phases, the disease is mostly asymptomatic. This section of the questionnaire has consistently been used to assess rehabilitation in dialysis patients [220]. In other words, after reaching the full picture of CKD and beginning RRT, the improvement of these scores would prove the success of therapy. As this was not the focus of this work, this data was not analysed.

Besides, there is evidence of a good correlation between the eight HRQoL domains analysed and all but three areas of that extended scale. These are quality of social interaction, social support and patient satisfaction [221]. Consequently, the expression of most

of those problems is safeguarded. Moreover, they add a lot of work and turn it harder to use in office context, thus not adequate as good simple sentinel tests for the right moment to start dialysis, before symptoms arise.

4.2.5 Endpoints

Five endpoints were considered: "Death", "Beginning of dialysis", "Hospital admissions" and "Emergency Room (ER) utilization". The first two for being dramatic events in a patient's life, the third and fourth as surrogates of worsening health problems and the last because it is considered the gold standard of CKD staging [21].

Follow-up time was 24 months. Endpoints "Death" and "Beginning of dialysis" were studied both as binaries (yes/no) within that period and as time to event. Endpoint "Hospital admission" was investigated under more than one perspective: counts of episodes, time to event and number of inpatient days (as a surrogate of severity) during observation period. For endpoint "ER usage", count of episodes during the same period and time to event were considered. All these four "hard" endpoints were considered as outcome events for survival analysis. Only the patients who survived and had not begun dialysis at 24 months were considered for statistical analysis regarding hospital admissions and emergency services usage.

4.2.6 Patients' Priorities and Preferences

Patients' priorities were an important concern in this study in order to rank endpoints. Participants were asked about their opinion regarding what their physician's priority should be, the question being formulated the following way: "My physician's priority should be… ", and choosing among six different options; "…that I don't dye"; "…that I don't need dialysis"; "…that my lab tests don't get worse"; "…that I don't need hospital admission"; "…that I don't need to go to ER"; "… that my general health doesn't get worse".

As it was very difficult for the patients to rank these 6 options using a Likert scale [222], questions were made asking each one against another in a championship-like grid (fig 7).

7. Neste momento a prioridade do meu médico deve ser evitar que...

7.1	☐	as **análises piorem**	OU	☐	entre em **diálise**
7.2	☐	tenha que ir ao **serviço de urgência**	OU	☐	que fique **internado**
7.3	☐	**piore e deixe de estar ativo**	OU	☐	que eu **morra**
7.4	☐	as **análises piorem**	OU	☐	tenha que ir ao **serviço de urgência**
7.5	☐	fique **internado**	OU	☐	que eu **morra**
7.6	☐	as **análises piorem**	OU	☐	que fique **internado**
7.7	☐	entre em **diálise**	OU	☐	**piore e deixe de estar ativo**
7.8	☐	tenha que ir ao **serviço de urgência**	OU	☐	que eu **morra**
7.9	☐	**piore e deixe de estar ativo**	OU	☐	que as **análises piorem**
7.10	☐	entre em **diálise**	OU	☐	que fique **internado**
7.11	☐	eu **morra**	OU	☐	que as **análises piorem**
7.12	☐	entre em **diálise**	OU	☐	tenha que ir ao **serviço de urgência**
7.13	☐	tenha que ir ao **serviço de urgência**	OU	☐	**piore e deixe de estar ativo**
7.14	☐	eu **morra**	OU	☐	que entre em **diálise**
7.15	☐	fique **internado**	OU	☐	**piore e deixe de estar ativo**

Figure 7 - Options for patients' priorities

Every alternative was opposed against all the others. (For example, patients were asked if they preferred that their physician's priority should be avoiding the beginning of dialysis, or avoiding hospitalizations; another question was if they preferred that their physician's priority should be to avoid their death or avoid the beginning of dialysis.) Fifteen choices were put to each participant, combining all possibilities among those six alternatives. Each alternative was challenged 5 times against different options. Each "victory" was awarded 1 point. If one choice won to all, it would score 5 points. On the other end, if an option lost against all others, it would have zero (0) points. Two variables were used for statistical analysis: firstly, the total number of points of each option computed for each patient, decoding the ranking assigned by him/her, as well as the intensity of the preferences; secondly, the percentage of patients that assigned each of the six alternatives as a rank (1st, 2nd, 3rd options, and so on, down to 6th and last option).

The alternative "avoid worsening of health condition" was deliberately left on this list although it has different characteristics. It is a multidimensional endpoint, a surrogate of Quality of Life (QoL), functionality and well-being, and may be useful as a calibrator for this scale, giving some insight into knowing the real meaning of each option to the patients. It was not considered as an endpoint for not having a definite variable that could represent it.

One patient refused to answer to this set of questions and this is why total number of answers to this item will be 59.

4.2.7 Statistical Analysis

Summary (descriptive) statistics were reported as mean and standard deviations, median and quartiles, where relevant for continuous variables and as counts and percentages for categorical variables.

Correlations (Spearman rank test) between the renal function estimations (CG, EPI, MDRD4 and MDRD6 formulae) were performed at baseline, 12 and at 24 months. The correlation between baseline and 24 months were also tested for prediction purposes.

To evaluate internal consistency of PROM, Cronbach's alpha [223] of PROMs scales: WHODAS, SWLS, SPPB and each one of the 8 domains of KDQoL was calculated. Also, correlation results between PROM scales and other numerical scales: Charlson_1987, Charlson_2011, eGFR scale, with binary category variables (gender, categorized age: ≤65 *versus* >65; labour situation: active *versus* retired, yearly income: ≤7000 € *versus* >7000 €, and schooling: less than primary school *versus* at least primary school) were established. Spearman rank test was used between two quantitative variables, while correlation point-bi-serial was used between one continuous variable and one binary category variable.

Linear regression models for the PROM prediction were also performed (linear coefficients, LC, and 95% Confidence Intervals, CI). Residuals analysis and testing for model significance were conducted. The multivariable analysis was performed only for the variables presenting $p \leq 0.05$.

For each time-to-event endpoint ("Death within 24 months", "Dialysis within 24 months", "Hospital Admissions within 24 months" and "ER episodes within 24 months"),

potential relationships (Hazard Ratios, HR, and 95% Confidence Intervals, CI) associated to the remaining different scales and demographic variables were explored in univariable analysis, using a Cox regression model. The multivariable analysis was performed only for the variables presenting at least $p \leq 0.05$ in the univariate model.

For the patients' priorities analysis, a one-way repeated measure was used to test mean score differences between patients' preferences ("that I don't die"; "that I don't need dialysis"; "that my lab tests don't get worse"; "that I don't need hospital admission"; "that I don't need to go to ER";" that my general health doesn't get worse"). The sphericity assumption was verified by Huynh-Feldt epsilon. Normality residuals were verified by visual QQ plot inspection. Comparison between independent groups was performed using the Mann-Whitney test.

All statistical analyses were performed using SPSS® Software, version 22.0 (SPSS, Inc., Chicago, IL) and p-values under 0.05 were considered significant.

4.3 Baseline Characterization of a CKD Population

4.3.1 Demographics

Baseline characteristics of participants (at the moment they answered to questionnaires and tests) are summarized in table 8. Average (mean) age was 67.43±14.19 years, with a median of 68.5, the first quartile 56.8 and the third quartile 79. Almost three quarters of the patients (71.7%) were retired. Due to the reduced size of the sample, other demographic variables were collapsed to two categories. For Education, 21,7% had less than Primary School and for Income, 28,3% had a yearly income of less than 7000 €.

Table 8 - Sample characterization at baseline (n=60)

	n (%)		n (%)
Gender		**Schooling**	
Male	31 (51.7)	Less than Primary School	13 (21.7)
Female	29 (48.3)	Complete Primary School	23 (38.3)
		Secondary School	12 (20.0)
Age		University degree	12 (20.0)
≤65	24 (40.0)		
]65;75]	15 (25.0)	**Yearly Income (€)**	
>75	21 (35.0)	≤7000	17 (28.3)
		]7000-20000]	37 (61.7)
Labour situation		>20000	6 (10.0)
Active	17 (28.3)		
Retired	43 (71.7)		

4.3.2 Comorbidities

Other health problems of participants were assessed by the Charlson Comorbidity Index (versions of both 1987 and 2011) and are summarized in table 9. This sample of CKD patients had a moderately low average score, well below 50% of the maximum, computed by both scales, suggesting that this may not be an important problem in these patients. The 2011 scale returned lower values, as compared with the 1987 value. There was, however, a high correlation between the two scales (Spearman rank coefficient was 0.692, $p<0.001$).

Table 9 - Charlson Comorbidity Index at baseline (n=60)

	Range	avg±sd	1st quartile	median	3rd quartile
Charlson Comorbidity Index (1987) (scale: 0-35 points + age)	(2-12)	7.03±2.42	5	7	9
Charlson Comorbidity Index (2011) (scale: 0-34 points)	(0-10)	2.35±2.90	0	1	3

4.3.3 Kidney Function

Table 10 shows absolute counts and percentages of patients in each CKD stage at baseline, as calculated by each one of the formulae. There are important differences of the CKD stages distribution according to eGFR of each formula. Stage 4 is the mode for CG, MDRD4 and MDRD6 formulae with respectively 50.0%, 58.3% and 60.0% of the patients, while CKD-EPI formula assigns more patients to stage 3 (53.3%). There are no stage 2 patients with both MDRD formulae, and MDRD4 is the one that returns the lowest values, allocating almost one third of the patients to stage 5, opposed to CKD-EPI, that only considers 5 patients (8.3%) as stage 5 patients. The distribution of patients by CKD stages, according to MDRD formulae, gives the "worse" picture of the sample, as far as CKD stages are concerned.

Considering values of eGFR, mean eGFR was 27.1±12.9, 31.2±12.8, 19.6±7.4 and 22.4±8.5, as computed, respectively, by CG, CKD-EPI, MDRD4 and MDRD6 formulae. Again, MDRD formulae yielded the lowest values, and CKD-EPI the highest.

Table 10 - Staging of renal function at baseline, according to the four formulae.

	n (%)		n (%)
CG stages		**MDRD4 stages**	
Stage 2	2 (3.3)	Stage 2	0 (0.0)
Stage 3	18 (30.0)	Stage 3	6 (10.0)
Stage 4	30 (50.0)	Stage 4	35 (58.3)
Stage 5	10 (16.7)	Stage 5	19 (31.7)
CKD-EPI stages		**MDRD6 stages**	
Stage 2	1 (1.7)	Stage 2	0 (0.0)
Stage 3	32 (53.3)	Stage 3	12(20.0)
Stage 4	22 (36.7)	Stage 4	36(60.0)
Stage 5	5 (8.3)	Stage 5	12(20.0)

Considering value of eGFR, mean eGFR was 27.1±12.9, 31.2±12.8, 19.6±7.4 and 22.4±8.5, as computed, respectively, by CG, CKD-EPI, MDRD4 and MDRD6 formulae. Again, MDRD formulae yield the lowest values, and CKD-EPI the highest.

4.3.4 Health Untoward Events in the Previous 12 Months

As shown in Figure 7, In the previous 12 months, 49 patients (81.67%) had no hospital admissions whereas 9 patients (15%) had at least one hospital admission episode (average 1.44± 0.73, range 1-3, median 1). During that period, a total of 13 hospital admission episodes were computed. Each episode lasted 12.56±14.04 days (range 2-41, median 4). The last discharge from hospital admission had been 121.00±97.23 days, before (range 20-323, median 122).

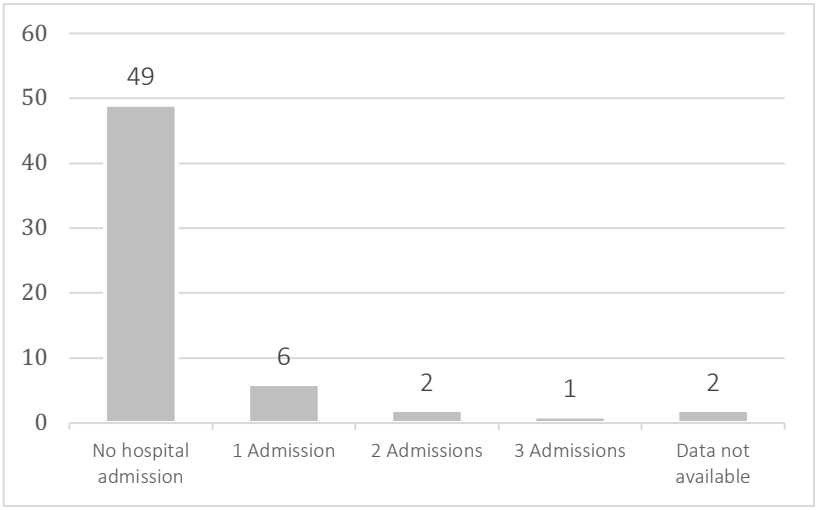


Figure 8 - Distribution of hospital admissions among patients in the previous year

For episodes of ER, 38 patients (63.33%) had no ER episodes in the previous year and 20 patients (33.33%) needed to go, at least once, to the ER, accounting for a total of 45 ER episodes (average 2.25±1.25, range 1-5, median 2) (Figure 8). Average time since last ER episode was 152.90±117.46 days (range 24-355, median 102).

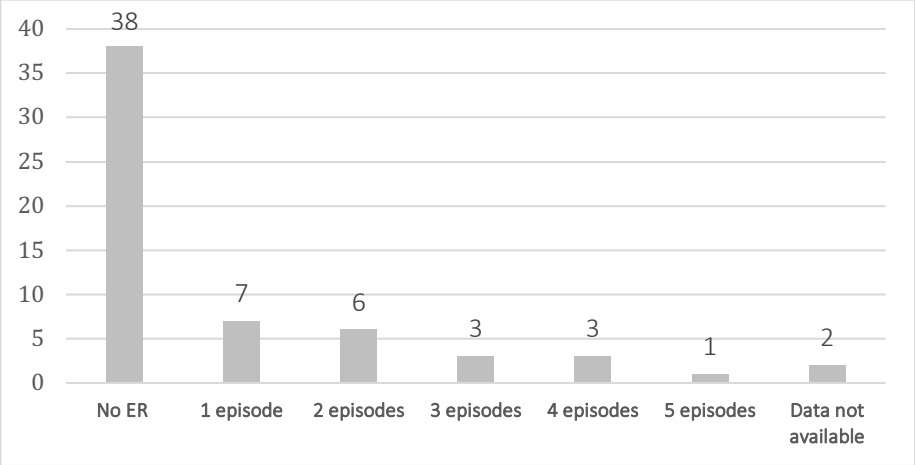


Figure 9 - Distribution of ER episodes among patients in the previous year

Two patients had a health plan that allowed them to be admitted to hospitals outside the NHS, so information about their hospital admissions and ER usage was unavailable.

4.4 Regarding Kidney Function Measurement, which eGFR Formula is more Useful at Predicting of Outcomes and Correlating with Well-Being?

4.4.1 Correlation Matrices Between eGFR Formulae

All eGFR formulae correlated with each other in all time points they were used. Spearman coefficients were all above 0.792 at Baseline, 0.603 at 12 months and 0.522 at 24 months. At baseline, all formulae presented high correlations between them. However, in other time points, correlation coefficients decreased, as shown in tables 11, 12 and 13.

Table 11 - Correlation matrix between eGFR at baseline

	CG	CKD-EPI (n=60)	MDRD4 (n=60)	MDRD6 (n=60)
CG	1	0.769***	0.792***	0.835***
CKD-EPI		1	0.884***	0.912***
MDRD4			1	0.966***
MDRD6				1

*Spearman rank correlation; *p<0.05; **p<0.01; ***p<0.001*

Table 12 - Correlation matrix between eGFR at 12 months

	CG	CKD-EPI (n=49)	MDRD4 (n=49)	MDRD6 (n=46)
CG	1	0.704***	0.612***	0.603***
CKD-EPI		1	0.881***	0.840***
MDRD4			1	0.856***
MDRD6				1

*Spearman rank correlation; *p<0.05; **p<0.01; ***p<0.001*

Table 13 - Correlation matrix between eGFR at 24 months

	CG	CKD-EPI (n=42)	MDRD4 (n=42)	MDRD6 (n=29)
CG	1	0.606***	0.552***	0.522**
EPI		1	0.925***	0.869***
MDRD4			1	0.884***
MDRD6				1

*Spearman rank correlation; *p<0.05; **p<0.01; ***p<0.001*

4.4.2 Evolution of kidney Function Through Time

It is interesting to look at the proportions of each CKD stage at three different time points according to different formulae: at baseline, at 12 months and at 24 months, depicted in Figure 9.

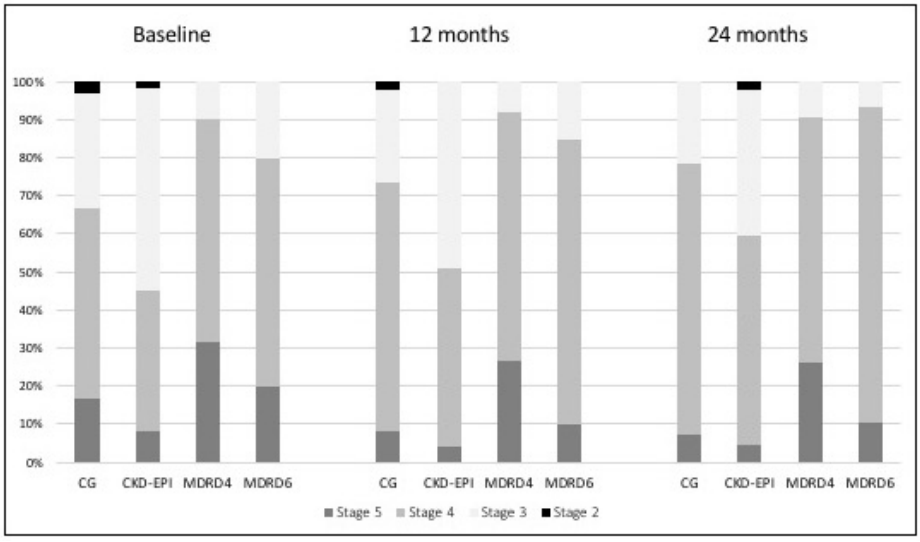


Figure 10 - Distribution of patients through CKD stages in three different time points

(Baseline (n=60); at 12 months (n=49); at 24 months (n=42))

Regardless the time point, MDRD formulae returned lower values of eGFR and increased the proportion of patients in CKD stages 4 and 5, and considerations made for baseline data remained valid. Regardless of the time point, there was clearly a different picture of the sample, depending of the used formula, as far as CKD stages were concerned.

The same happened when raw values of eGFR were evaluated. At 12 months after baseline, mean eGFR was 27.2±12.3, 31.5±11.6, 19.8±6.8 and 23.0±8.2, when computed, respectively, by CG, CKD-EPI, MDRD4 and MDRD6 formulae. At 24 months, mean eGFR was 25.5±9.4, 31.2±13.1, 19.3±7.8 and 19.5±5.8, when computed, respectively, by CG, CKD-EPI, MDRD4 and MDRD6 formulae.

Another remarkable finding was that, regardless of the formula used to stage patients, more than half of the patients who survived or did not begin dialysis after 24 months, remained at the same CKD stage (Table 14).

Table 14 - Evolution of CKD stages from baseline to 24 months (n=42)

	CG	CKD-EPI	MDRD 4	MDRD 6
	n (%)	n (%)	n (%)	n (%)
Improved CKD stage	4 (9.5)	3 (7.1)	5 (11.9)	0 (0)
Did not change CKD stage	21 (50.0)	22 (52.4)	27 (64.3)	24 (57.1)
Worsened CKD stage	17 (40.5)	17 (40.5)	10 (23.8)	5 (11.9)
Missing data				13 (31.0) *

(missing data refers to serum albumin result which was not available for these 13 patients at 24 months)*

4.4.3 Prediction of CKD Stage Evolution Through Time

Table 15 shows the correlation between baseline and 24 months eGFR, highlighting the correlation of the values of the same formula and showing the higher level of correlation for CG.

Table 15 - Correlation results between eGFR at Baseline and 24 months

	24 months			
	CG (n=42)	CKD-EPI (n=42)	MDRD4 (n=42)	MDRD6 (n=29)
Baseline CG	**0.507*** **	-0.007	-0.040	-0.031
Baseline CKD-EPI	0.333*	**0.398** **	0.425**	0.459*
Baseline MDRD4	0.282	0.379*	**0.417** **	0.423*
Baseline MDRD6	0.345*	0.385*	0.389*	**0.471***

*Spearman rank correlation; *p<0.05; **p<0.01; ***p<0.001*

Correlations between kidney function measurements at baseline and at 24 months, was weak to moderate, the highest being the one given by CG formula. On the other hand, there is no predictive value of eGFR as calculated by CG formula to others. Data suggested a higher proximity between CKD-EPI, MDRD 4 and MDRD6, and a weaker correlation to CG and to each other through time.

As presented in section 4.6. (table 20), only CG formula was able to demonstrate a significant relationship for PROM, namely SPPB, WHODAS and KDQoL_PF, with a linear coefficient of 0.083 for SPPB, -0.224 for WHODAS, and 0.008 for KDQoL_PF ($p<0.05$ for all).

It didn't show any significant relationship with the other tests. Also, all the other formulae showed no significant relationships for all PROM tests.

As presented in section 4.7.1. (table 24), it was found that CG formula could predict mortality within 24 months with HR of 0.904) and all formulae could predict the beginning of dialysis within 24 months with HR of 0,715; 0.726; 0.789 and 0.849 respectively for MDRD4, MDRD 6, CG and CKD-EPI.

4.5 How do PROM Represent a CKD Population? How does a CKD population Perform as far as PROM are Concerned?

4.5.1 Patient Reported Outcome Measures (PROM)

Scores (average, standard deviation, median, first and third quartile) of all dimensions of questionnaires are displayed in table 16.

Table 16 - Raw results of PROM (n=60)

	units	avg±sd (%)	range	1st quartile (%)	Median (%)	3rd quartile (%)
SPPB	0-12	7.4±3.4 (62)	0-12	4 (33)	8 (67)	10 (83)
SWLS	5-35	25.6±7.5 (69)	6-35	21 (53)	27 (73)	32 (90)
WHODAS	12-60	20.0±9.8 (17)	12-47	13 (2)	15.5 (7)	23.25 (23)
KDQoL_PF	0-1	0.64±0.32	0-1	0.35	0.75	0.95
KDQoL_RP	0-1	0.78±0.30	0-1	0.5	1	1
KDQoL_Pain	0-1	0.69±0.35	0-1	0.42	0.78	1
KDQoL_GH	0-1	0.47±0.19	0-1	0.30	0.50	0.60
KDQoL_VT	0-1	0.50±0.25	0-0.94	0.31	0.50	0,70
KDQoL_SF	0-1	0.84±0.20	0-1	0.72	1	1
KDQoL_RE	0-1	0.84±0.27	0-1	0.75	1	1
KDQoL_MH	0-1	0.65±0.26	0-1	0.45	0.70	0.90

Figure 10 shows a comparison in all PROM scales in a normalized way. It is clear that KDQoL_RP, Pain, KDQoL_RE and KDQoL_MH show a ceiling effect, as half of the patients had maximum scores. For the other variables, the median was high (or very low, in the case of WHODAS, as this scale is inverted).

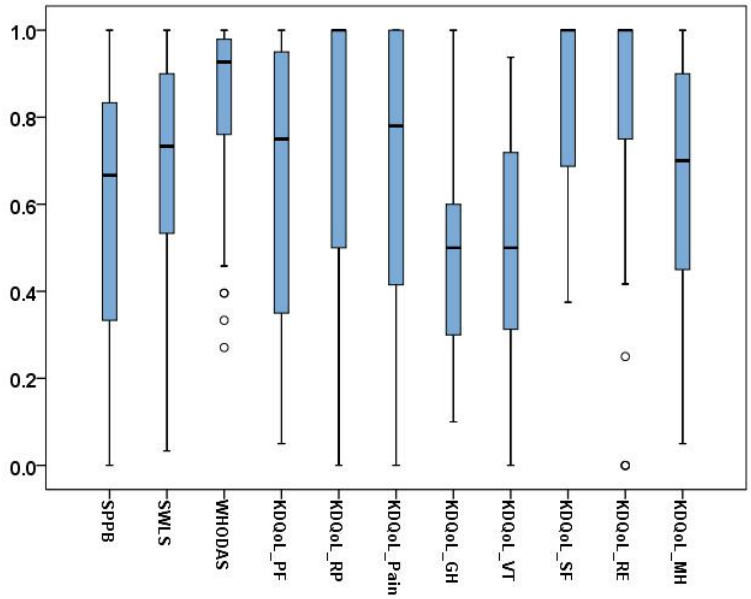


Figure 11 - Boxplots of the PROMS scales

(scale is standardized between 0 and 1 and WHODAS is in reverse scale)

This is suggestive that the general status of this sample of patients was good and it also shows that the several PROM did not progress simultaneously, understandably so, because they measure different constructs.

4.5.2 Score of PROM in the several to CKD Stages

Table 17 shows the scores of PROM for each CKD stage, according to several eGFR formulae. No statistical inference was drawn, due to the small size of some groups. However, in some cases, highlighted in grey, these seems to be a continuous tendency of variation downwards (or upwards in the case of WHODAS) in line with advancing kidney function. Curiously, the groups of data highlighted in dark grey were the ones for which a univariate linear regression model was found, as shown in Table 20.

Table 17 - Scores of PROM through CKD stages

formula	stage	n	SPPB	SWLS	WHODAS	KDQoL_PF	KDQoL_RP	KDQoL_Pain	KDQoL_GH	KDQoL_VT	KDQoL_SF	KDQoL_RE	KDQoL_MH
CG	Stage 2	2	11.0±1.4	24.0±8.5	13.5±2.1	0.98±0.04	0.59±0.22	0.72±0.00	0.73±0.04	0.59±0.31	0.88±0.18	1.00±0.00	0.83±0.18
	Stage 3	18	8.3±3.6	26.6±7.3	16.3±8.4	0.78±0.29	0.87±0.27	0.67±0.32	0.43±0.20	0.56±0.25	0.82±0.23	0.85±0.29	0.70±0.31
	Stage 4	30	7.3±3.1	25.2±8.4	20.9±9.3	0.57±0.30	0.77±0.30	0.66±0.39	0.47±0.19	0.48±0.26	0.84±0.19	0.86±0.19	0.64±0.23
	Stage 5	10	5.6±3.6	25.4±5.9	25.2±11.9	0.54±0.37	0.69±0.34	0.77±0.32	0.50±0.20	0.46±0.25	0.90±0.18	0.73±0.42	0.55±0.26
CKD-EPI	Stage 2	1	10.0	18.0	15.0	0.95	0.75	0.72	0.70	0.38	0.75	1.00	0.70
	Stage 3	32	7.8±3.4	26.3±8.9	18.3±8.0	0.65±0.30	0.83±0.26	0.67±0.38	0.45±0.19	0.53±0.26	0.82±0.21	0.86±0.25	0.67±0.27
	Stage 4	22	6.8±3.4	25.5±6.1	22.0±11.7	0.61±0.37	0.74±0.35	0.73±0.31	0.50±0.21	0.49±0.26	0.85±0.19	0.83±0.26	0.64±0.26
	Stage 5	5	7.2±4.5	22.8±1.6	22.8±11.8	0.63±0.36	0.66±0.33	0.62±0.39	0.46±0.16	0.41±0.24	0.98±0.06	0.72±0.44	0.56±0.20
MDRD4	Stage 2	0	-	-	-	-	-	-	-	-	-	-	-
	Stage 3	6	7.8±5.1	22.5±7.3	20.5±12.6	0.65±0.43	0.82±0.20	0.73±0.24	0.58±0.13	0.41±0.26	0.71±0.26	0.83±0.30	0.55±0.22
	Stage 4	35	8.2±3.0	25.9±8.4	17.8±7.7	0.69±0.43	0.83±0.27	0.66±0.37	0.44±0.19	0.54±0.26	0.85±0.19	0.87±0.22	0.68±0.27
	Stage 5	19	5.9±3.3	26.0±5.9	23.8±11.5	0.54±0.33	0.69±0.33	0.72±0.34	0.50±0.21	0.46±0.24	0.88±0.18	0.79±0.34	0.62±0.26
MDRD6	Stage 2	0	-	-	-	-	-	-	-	-	-	-	-
	Stage 3	12	7.2±4.3	26.5±6.7	19.0±9.7	0.65±0.34	0.70±0.31	0.78±0.26	0.48±0.22	0.45±0.26	0.76±0.21	0.83±0.34	0.64±0.27
	Stage 4	36	8.1±3.0	25.3±8.4	18.4±8.2	0.68±0.31	0.87±0.22	0.63±0.38	0.47±0.19	0.54±0.25	0.85±0.19	0.87±0.18	0.68±0.26
	Stage 5	12	5.6±3.3	25.4±5.7	25.7±12.6	0.53±0.35	0.59±0.38	0.75±0.33	0.47±0.21	0.43±0.25	0.90±0.18	0.77±0.39	0.57±0.25

4.5.3 Evaluation of Internal Consistency of the Questionnaires

Table 18 shows Cronbach's alpha for the questionnaires, both for this study and other studies used for comparison. In this study, all scales demonstrated reliability, according to this criterium (Cronbach's alpha >= 0.6) [224], with the exception of KDQoL_SF, which showed little consistency, presenting a Cronbach alpha of 0.315. This may have been due to the small size of the sample or to the fact that it is only composed of two questions. It may also have been due to a problem in the Portuguese version of the questionnaire: this domain is the one that presents the lower indices of internal consistency in more than one validation tests we could find for the Portuguese language. On the contrary, it didn't happen in the validation of the original test in English. Due to this fact, all results related to this variable must be read with caution, as this may not be representative of the construct for which it was created. Also, KDQoL_GH has shown borderline consistency according to this criterium (0.605), which is acceptable, provided that results are interpreted with caution and taken into consideration in the context of the calculation.

Table 18 - Cronbach's Alpha of the questionnaires

	Cronbach's Alpha				
	Our study (CKD)	**Portuguese validation (HD) Ferreira, 2000 [188]**	**Brazilian (HD) Moreira, 2009 [225]**	**Brazilian (CKD and HD) Duarte, 2005 [226]**	**Original version (HD) Hays, 1994 [165]**
WHODAS 12 items	0.895	-	-	-	-
SPPB	0.783	-	-	-	-
SWLS	0.863	-	-	-	-
KDQoL					
KDQoL_PF	0.944	0.873	0.9	0.895	0.92
KDQoL_RP	0.963	0.751	0.9	0.641	0.87
KDQoL_Pain	0.908	0.844	0.9	0.666	0.87
KDQoL_GH	**0.605**	0.875	0.7	0.717	0.78
KDQoL_VT	0.873	0.826	0.7	0.714	0.90
KDQoL_SF	**0.314**	**0.603**	**0.7**	**0.598**	**0.87**
KDQoL_RE	0.972	0.710	0.9	0.616	0.86
KDQoL_MH	0.864	0.645	0.8	0.765	0.80

4.5.4 Correlation Matrix Between PROM

Table 19 shows the correlation matrix between all PROM studied (SPPB, SWLS, WHODAS and KDQoL).

Among the 11 PROM tested, we found 12 highly significant correlations ($p<0.001$), the highest Spearman correlation coefficient being presented between KDQoL_PF and both WHODAS and SPPB (-0.850 and 0.850, respectively). We found a slightly lower value between WHODAS and SPPB (-0.799). The domain with the largest number of correlations with high significance is KDQoL_VT: KDQoL_MH (0.719), WHODAS (-0.605), KDQoL_PF (0.580). SPPB (0.557) and KDQoL_RE (0.516). The other highly significant correlations were found between KDQoL_MH and KDQoL_RE (0.599); between WHODAS and KDQoL_MH (-0.534) and between WHODAS and KDQoL_RP (-0.466). There were 17 other significant relationships with weaker correlations.

Although we could find a significant negative correlation between KDQoL_SF and KDQoL_Pain (-0.559), this must be looked at with extreme caution because tests of internal consistency didn't support that KDQoL_SF expresses the construct of good social function strongly enough. Moreover, it makes no sense that the less pain (better score) would harm social function, or the other way around.

On the other hand, KDQoL_GH had no significant correlation with any other PROM. The near-limit value of internal consistency for this variable may explain this result.

SWLS also had few (and weaker) correlations with other PROM.

Table 19 - Correlation matrix between all PROM studied

	SPPB	SWLS	WHODAS	KDQoL							
				PF	RP	Pain	GH	VT	SF	RE	MH
SPPB	1	0.008	**-0.799*** **	**0.850*** **	0.384**	-0.324*	0.131	**0.557*** **	0.346**	0.266*	0.326*
SWLS		1	-0.095	0.011	0.137	-0.154	-0.055	0.276*	0.181	0.223	0.385**
WHODAS			1	**-0.850*** **	**-0.466*** **	0.195	-0.086	**-0.605*** **	-0.296*	-0.291*	**-0.534*** **
KDQoL_PF				1	0.390**	0.271*	0.166	**0.580*** **	0.394**	0.252	0.407**
KDQoL_DP					1	0.176	0.010	0.452**	0.073	0.432**	0.425**
KDQoL_Pain						1	0.015	0.295*	**-0.559*** **	-0.121	-0.224
KDQoL_GH							1	0.006	0.235	-0.014	-0.084
KDQoL_VT								1	0.250	**0.516*** **	**0.719*** **
KDQoL_SF									1	-0.044	0.130
KDQoL_RE										1	**0.599*** **
KDQoL_MH											1

*Spearman rank correlation; *p<0.05; **p<0.01; ***p<0.001; highly significant correlations highlighted in bold*

4.6 What are the Most Important Predictors of PROM in a CKD Population?

Table 20 shows linear regression models for SPPB, WHODAS, KDQoL_PF, KDQoL_RP, KDQoL_VT and KDQoL_RE. For SPPB, significant positive variables were labour situation (active), schooling (more educated), age (younger), less comorbidities (by both formulae) and higher eGFR (only when calculated by CG formula). For WHODAS, significant negative variables (less disabled) were gender (men), labour situation (active), age (younger), less comorbidities (by Charlson_1987) and higher eGFR (only when calculated by CG formula). For KDQoL_PF, significant positive variables were gender (men), labour situation (active), schooling (more educated), age (younger), less comorbidities (by both formulae) and higher eGFR (calculated by CG formula). For KDQoL_RP and KDQoL_VT, the only significant positive variable was less comorbidities (by Charslon_1987). For KDQoL_RE, significant positive variables were labour situation (active) and age (younger).

Table 20 - Univariate linear regression models for the several PROM

	SPPB	WHODAS	KDQOL_PF	KDQOL_RP	KDQOL_VT	KDQOL_RE
Gender						
Male	ns	-6.039 [-10.884; -1.194]	0.213 [0.053;0.372]	ns	ns	ns
Labour situation						
Retired	-3.828 [-5.542; -2.113]	7.774 [2.503;13.046]	-0.302 [-0.472; -0.133]	ns	ns	-0.157 [-0.307; -0.008]
Schooling						
> Primary	2.812 [0.767;4.856]		0.300 [0.111;0.489]	ns	ns	ns
Age (years)	-0.154 [-0.203; -0.105]	0.361 [0.207;0.515]	-0.015 [-0.019; -0.010]	ns	ns	-0.005 [-0.010; -0.001]
Comorbidities						
Charlson_1987	-0.826 [-1.130; -0.523]	1.980 [1.056;2.905]	-0.081 [-0.109; -0.053]	-0.032 [-0.063; -0.001]	-0.034 [-0.060; -0.008]	ns
Charlson_2011	-0.342 [-0.640; -0.040]	ns	-0.032 [-0.060; -0.004]	ns	ns	ns
eGFR						
CG	0.083 [0.017;0.150]	-0.224 [-0.413; -0.034]	0.008 [0.002;0.015]	ns	ns	ns

Units: Linear coefficient and 95% CI ($p<0.05$ for all values presented; ns: non-significant)

For the remaining PROM (SWLS, KDQoL_Pain, KDQoL_GH, KDQoL_SF and KDQoL_MH), no regression model could be found. Income, eGFR (computed by CKD-EPI, MDRD4 and MDRD6 formulae), as well as the number of hospital admissions and ER episodes in the last year didn't show any significant linear regression models to predict PROM. Also, for last year's health untoward events, no regression model could be found.

In multivariate analysis, age was a significant determinant for SPPB, WHODAS and KDQoL_PF (linear coefficients and CI 95%: -0.137 [-0.197; -0.078], 0.330 [0.161; 0.499] and -0.013 [-0.018; -0.007]) and male gender was significant for WHODAS and KDQoL_PF (HR and CI 95% respectively -4.553 [-8.935; -0.172] and 0.151 [0.021;0.282]). In other words, older patients performed worse in KDQoL_PF, SPPB, WHODAS, and men performed better in WHODAS and KDQoL_PF.

4.7 What is the Impact of Baseline Variables on Future Endpoints and How PROM can Predict Those Endpoints?

Tables 21 and 22 show data related to endpoint variables during 24 months of follow-up:

Table 21 - Time to first event (n=59)

	Number of patients n	Time to first event (months) avg±sd	Median (months)	Range (months)
Death	8	13.13±7.97	11.42	2-22
Dialysis	10	10.34±7.62	7.07	1-23
Hospital Admission	16	10.92±4.96	10.78	2-21
ER episode	30	9.49±7.10	9.56	1-22

During the follow-up period, 4 patients died and 6 patients began dialysis during the first year. In the second year, 4 died and another 4 began dialysis.

There were 22 hospital admissions, which corresponded to a total of 305 inpatient days (average 30.50±26.5, range 1-82, median 33). This is about 1% of the patient-days at risk for the same period. Data related to hospital admissions and ER usage is presented in table 22. One patient had a different health plan and also used another hospital. Therefore, data of hospital admissions and ER episodes is not presented.

Table 22 - Hospital Admissions and ER episodes at 24 months (n=42)

	Number of patients	Number of Episodes	Number of episodes per subject		
	n (%)	n	avg±sd	range	median
Hospital Admissions					
0	31 (73.81)				
> 0	10 (23.81)	22	2.00±1.32	1-5	2
ER Episodes					
0	17 (40.48)				
> 0	24 (57.14)	96	4.00±6,76	1-35	2
No Hospital Admissions and no ER episodes	16 (38.10)				

Some predictive values of baseline variables for study endpoints could be found and are presented in table 23:

- for endpoint “Death within 24 months”, significant risk determinants were: higher age, lower income, lower schooling, higher comorbidity index (by both scales), and lower eGFR (only for CG scale);
- for endpoint “Beginning dialysis within 24 months”, significant risk predictors were higher comorbidity index (measured by Charlson_2011) and lower eGFR (regardless the formula used);
- for endpoint “Hospital admissions within 24 months”, the only risk predictor with significant influence was higher comorbidity index (measured by both scales);

- for endpoint "ER episodes within 24 months", significant risk predictors were lower schooling and higher comorbidity index (measured by Charlson_2011);
- no significant predictive value could be found for Gender and Labour Situation.

Table 23 - Effect of studied variables on the study endpoints

	Mortality (HR)	**Dialysis (HR)**	**Hospital Admissions (HR)**	**ER Episodes (HR)**
Age (years)	1.139 [1.025;1.206]	ns	ns	ns
Income (€/year)				
≤7000	5.071 [1.210;21.248]	ns	ns	ns
Schooling				
< Primary School	4.312 [1.075;17.293]	ns	ns	2.578 [1.118;5.942]
Comorbidities				
Charlson_1987	1.416 [1.023;1.961]	ns	1.290 [1.029;1.616]	ns
Charlson_2011	1.236 [1.027;1.486]	1.168 [1.000;1.395]	1.245 [1.062;1.460]	1.153 [1.017;1.308]
eGFR				
CG	0.904 [0.824;0.991]	0.789 [0.687;0.904]	ns	ns
CKD-EPI	ns	0.849 [0.767;0.938]	ns	ns
MDRD4	ns	0.715 [0.591;0.867]	ns	ns
MDRD6	ns	0.726 [0.610;0.865]	ns	ns

(Univariate model. units: Hazard ratio: HR, CI95%; p<0.05; ns: non-significant)

Likewise, some predictive value of PROM to study endpoints was found: it is presented in table 24. SPPB, WHODAS, KDQoL_PF and KDQoL_RE have shown to significantly predict endpoint "death within 24 months"; SPPB, WHODAS and KDQoL_RP could predict endpoint "beginning of dialysis within 24 months"; SPPB, KDQoL_PF, KDQoL_VT and KDQoL_MH have predictive value to endpoint "hospital admissions within 24 months"; KDQoL_MH predicts endpoint "ER episodes within 24 months".

On the contrary, SWLS and KDQoL_SF, KDQoL_Pain and KDQoL_GH didn't show any predictive ability, regarding these endpoints.

Table 24- Predictive value of PROM on the study endpoints

	Mortality (HR)	Dialysis (HR)	Hospital Admissions (HR)	ER Episodes (HR)
PROM scores				
SPPB	0.761 [0.618;0.937]	0.824 [0.686;0.991]	0.833 [0.720;0.965]	ns
WHODAS	1.088 [1.024;1.155]	1.052 [1.000;1.108]	ns	ns
KDQoL_PF	0.075 [0.008;0.686]	ns	0.172 [0.037;0.794]	ns
KDQoL_RP	ns	0.137 [0.024;0.786]	ns	ns
KDQoL_VT	ns	ns	0.029 [0.003;0.273]	ns
KDQoL_RE	0.071 [0.008;0.605]	ns	ns	ns
KDQoL_MH	ns	ns	0.106 [0.015;0.759]	0.234 [0.054;1.000]

(Univariate model. units: Hazard ratio: HR, CI95%; p<0.05; ns: non-significant)

For Hospital admissions, multivariate analysis revealed a HR of 0.034 (IC95% [0.002; 0,723], p=0.03) for KDQoL_VT; and for emergency services usage, there was a HR of 2.671 (IC95% [1.148;6.213], p<0.05) for lower schooling. No multivariable model could be found for mortality and dialysis within 24 months.

4.8 What are Patients' Priorities Concerning their Treatment? What Are Their Preferences Regarding What Their Physicians First Concerns Should Be?

Table 25 shows the overall preferences of patients to what their physician's priority should be, among the six proposed options.

Avoidance of death has emerged as the top priority they require from their physician. If a general hierarchy was to be defined, data suggested the following: first "avoiding death";

second "avoiding dialysis" and "worsening of laboratory test"s (*ex-aequo*); then "avoiding worsening of general health" and "avoid hospital admissions" (*ex-aequo*); finally "avoiding the need to go to ER", as illustrated in Figure 11:

Table 25 - Preferences of patients about their physician's priorities

"My physician's priority should be…"	avg ± sd[1]	range	1st quartile	Median	3rd Quartile
… that I don't die	4.0±1.5***	0-5	3	5	5
… that I don't need dialysis	2.9±1.3***	0-5	2	3	4
… that my lab tests don't get worse	2.6±1,2***	0-5	2	3	3
… that my general health doesn't get worse	2.2±1.6***	0-5	1	2	3.5
… that I don't need hospital admissions	1.9±1.0***	0-4	1	2	3
… that I don't need to go to ER	1.2±1.3***	0-5	0	1	2

*(n=59; one patient refused to answer this question; unit: points, computed as explained in section 4.2.6.; ***p<0.001;*

[1] One-way repeated measures: $F_{H\text{-}F}(4.59;270.96) = 26.840$; p<0.001.

Interindividual variation coefficients were 36%, 42%, 44%, 72%, 49% and 100%, respectively for the alternatives "…that I don't die", "…that I don't need dialysis", "…that my lab tests don't get worse", "…that my general health doesn't get worse", "…that I don't need hospital admissions" and "… that I don't need to go to ER". This shows an increasing dispersion of answers from the first to the last option, with the exception of the already mentioned more subjective "worsening of general health".

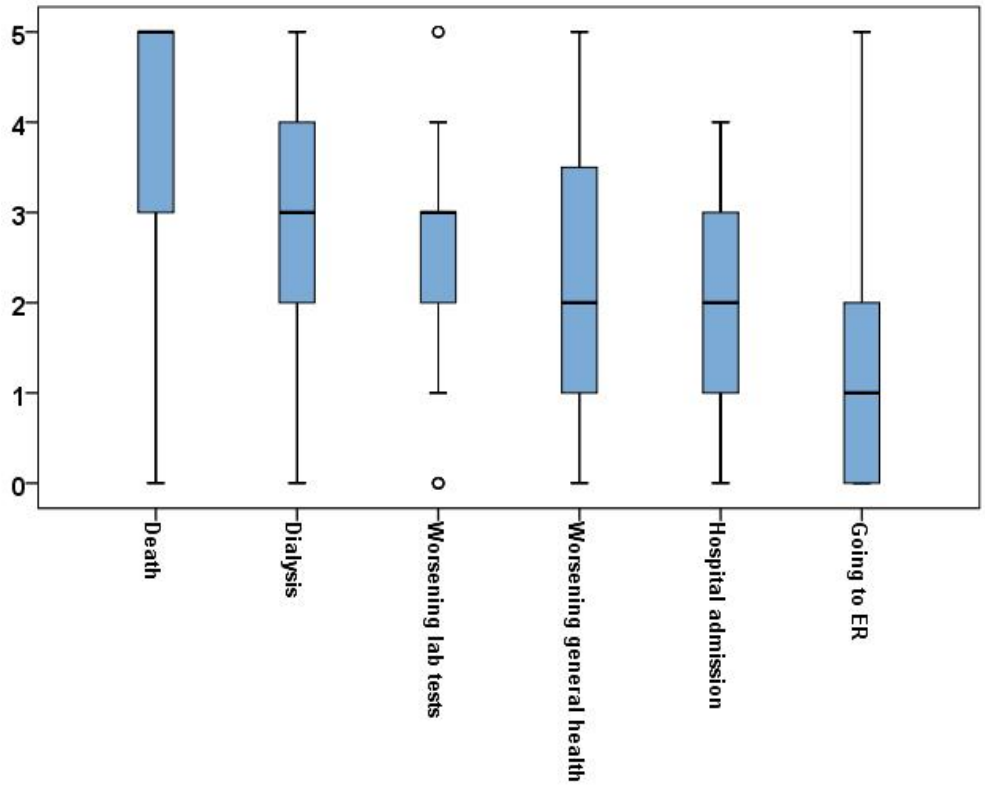


Figure 12 - Hierarchy of patients' preferences their physicians' about priorities

Another way of presenting this data is to consider the percentage of patients for each alternative preference at each place in the ranking of options (Table 26). Numbers highlighted in bold enhance the positions assigned by at least 50% of the patients. It draws a approximate diagonal pattern, similar to the bars that can be seen in figure 11.

Table 26 - Patients' preferences expressed as order of option

	Avoid death	Avoid dialysis	Avoid worsening of lab tests	Avoid worsening of general health	Avoid hospital admissions	Avoid ER episodes
1st option	**61,0%**	1,7%	5,1%	6,8%	0,0%	1,7%
2nd option	11,9%	**39,0%**	16,9%	**18,6%**	3,4%	6,8%
3rd option	11,9%	**30,5%**	**33,9%**	**18,6%**	25,4%	5,1%
4th option	6,8%	15,3%	**30,5%**	**22,0%**	**33,9%**	20,3%
5th option	3,4%	6,8%	8,5%	11,9%	**33,9%**	**33,9%**
6th option	5,1%	6,8%	5,1%	**22,0%**	3,4%	**32,2%**

Numbers highlighted in bold represent the ones that together sum more than half of the patients.

While the first option was clearly assigned to "avoid death" (61%), the other places of the hierarchy are not so evident. The other options need at least two options to reach 50% of the answers and there is some overlap between them, meaning that patients are not so sure of their answers.

The order of preferences was not very different from one group another. However, small specificities occurred and it is worthy to look closer to the hierarchy assigned by the different groups, as shown in table 27 shows the scores of patient's preferences for each studied baseline variable as discriminator. Significant differences are worthy a mention. Men gave a higher score to "avoid worsening of lab tests" than women (2.9±1.1 vs. 2.3±1.3). Active patients gave more points to "avoid worsening of general health" than retired ones (2.8±1.5 vs. 1.9±1.6). Low income patients also gave a high punctuation to "avoid death" than high income patients (4.7±0.7 vs. 3.7±1.7).

Table 27 - Hierarchy of patients' preferences about physicians' priorities

	Avoid death	Avoid dialysis	Avoid worsening of lab tests	Avoid worsening of general health	Avoid hospital admissions	Avoid ER episodes
	avg±sd	avg±sd	avg±sd	avg±sd	avg±sd	avg±sd
Gender						
Male (n=30)	4.0±1.4	3.0±1.3	2.9±1.1*	2.0±1.4	1.9±1.3	1.2±1.3
Female (n=29)	4.0±1.7	2.8±1.3	2.3±1.3*	2.3±1.8	1.9±1.3	1.2±1.3
Age						
≤65 (n=24)	4.0±1.8	3.0±1.3	2.8±1.2	2.4±1.6	1.7±0.7	1.1±1.2
>65 (n=35)	4.0±1.4	2.8±1.3	2.4±1.2	2.0±1.6	2.0±1.1	1.3±1.3
Labour situation						
Active (n=17)	3.9±1.8	3.0±1.3	2.7±1.4	2.8±1.5*	1.5±0.7	1.0±1.2
Retired (n=42)	4.0±1.4	2.8±1.3	2.6±1.1	1.9±1.6*	2.0±1.0	1.3±1.3
Income (€/year)						
≤7000 (n=17)	4.7±0.7*	2.7±1.6	2.7±0.8	2.2±1.6	1.8±1.0	0.9±0.8
>7000 (n=42)	3.7±1.7*	2.9±1.2	2.6±1.3	2.2±1.6	1.9±1.0	1.4±1.4
Schooling						
<Primary School (n=12)	4.2±1.5	2.8±1.6	2.5±1.1	1.5±1.5	1.6±1.1	1.2±1.2
>Primary School (n=47)	3.9±1.6	2.9±1.2	2.6±1.3	2.3±1.6	2.0±0.9	1.2±1.3

*(unit: points, as explained in section 5.2.6.; *p<0.05; n=59: one patient refused to answer)*

Although every sub-group assigned the first priority to avoidance of death, the highest score of all was given by poorer patients (4.7±0.7) and the lowest by richer patients (3.7±1.7), immediately followed by more educated (3.9±1.6) and active patients (3.9±1.8).

Regarding other endpoints and positions in this hierarchy, there is no clear preference for the second place between "avoiding dialysis" and "worsening of lab tests", especially in males (3.0±1.3 vs. 2.9±1.1) and poorer patients (2.7±1.6 vs. 2.7±0.8). Also, there was some overlapping between "avoiding worsening of lab tests" and "avoiding worsening of general health" in females (2.3±1.3 vs. 2.3±1.8), active patients (2.7±1.4 vs. 2.8±1.5) for the third place, as well as between "avoiding worsening of general health" and "avoid hospital admission" in males (2.0±1.4 vs 1.9±1.3), patients over 65 (2.0±1.6 vs. 2.0±1.1) and less educated patients (1.5±1.5 vs. 1.6±1.1) for the fourth place.

A deeper analysis returned interesting data for sub-groups. They ranked the available options roughly the same way, with some exceptions:

Firstly, men valued "Avoid worsening of lab tests" more than women (2.9±1,1 vs. 2.3±1.3 points), but not enough to invert their priorities as a whole. Women gave roughly the same importance to "Avoid worsening of general health" and "Avoid worsening of lab tests" (2.3±1.3 vs. 2.3±1.8). More testing is needed to assess if this is consistent with a different importance given by women to laboratory tests.

Older patients ranked all options the same way as younger people did, except for fourth place, for which they did not separate "Avoid worsening of general health" and "Avoid hospital admissions", meaning probably that they have perceived these alternatives as equivalent.

Active patients gave a higher rate to "Avoid worsening of general health" than retired ones (2.8±1.5 vs. 1.9±1.6). Active patients assigned the second place to this objective, overtaking "worsening of lab tests" (2.8±1.5 vs. 2.7±1.4).

Poorer patients had two extreme results: the highest score, given to "Avoid death" (4.7±0.7) and the lowest one, "Avoid going to ER" (0.9±0.8). They also gave the second preference *ex-aequo* to "Avoid dialysis" and "Avoid worsening of lab tests".

Less educated patients did not differentiate between the alternatives "Avoid worsening of general health" and "Avoid hospital admissions" (1.5±1.5 vs. 1.6±1.1) which

are in a tie, for the fourth place. They had the highest usage or ER services (a 2.5-fold increase in comparison with more educated ones), probably meaning that they did not perceive this behaviour as an indicator of a worse health status or a poorer quality of life and arguing against its inclusion of a surrogate of a worse quality of life in a model, in particular for this sub-group of patients.

5 Discussion

The traditional model of medical practice, in which the patient seeks the physician for an episodic consultation composed of a medical interview, a physical examination and followed by a one-way communication relating to diagnosis, treatment and prognosis, now faces increasing challenges.

Firstly, because people are getting older and prevalence of chronic diseases is increasing, contacts between physicians and patients have become long lasting relationships, a rather than episodic contacts. Patients and their families generally have much easier access to the physicians.

Secondly, because there is a reasonable probability that these patients with chronic diseases do not always see the same physician every time they need health services. Technological developments and market conditions are making individual medical practice offices less clinically effective. Most medical work is now carried out in larger collective medical environments with intervention of several professional groups.

Thirdly, because careful, exhaustive, medical appointments take time, there is a need for more efficient ways of characterizing conditions and guiding patients are needed.

Fourthly, because the processes of diagnosis and follow-up of chronic patients generates data of diverse relevance there is a need for objective indicators of performance to distinguish the wheat from the chaff.

Finally, because patients and families have almost open access to information and have access to the resources needed to challenge physicians' verdicts and confront them directly with their opinions [227] [228]. Therefore, the time for information asymmetry and full power of the physician (who orders) and the patient and families (who blindly obey) is no longer acceptable, both on ethical and practical grounds [229]. Prescription and expert advice may now be the object of negotiation [230] and for that, the demand for accountability is at a higher level than ever. This emphasises the need for objective reliable information which is easily understandable and transmissible to the patient.

Nevertheless, this new paradigm doesn't change the essential situation: the physician (often a team of physicians, nurses and other health professionals), together with

the patient and families or informal caregivers must work as a team to define a strategy with clear processes and goals, so that the remaining time of life of the patient can be enjoyed as well as possible, together with that of the family [231] [232]. Each one has a specific role in this setting: the physician gives advice based on the available medical evidence and on his professional experience, families provide the context and the patient has the final choice regarding the several options that arise from the discussion. Incorrect management of expectations is often a cause of stress and unhappiness, and the patient and family must learn to deal with the upcoming problems [233]. A plan of action should, thus, be developed that is clear to all participants.

This enhances the need for a common, fully adopted language and vocabulary between all stakeholders, that will guide everyone through the successes and failures without losing hope. This winding road has to be accepted by the patient as fundamental and the achievement of each following milestone must be used as an opportunity to celebrate or, in failures, and if pertinent, to change plans towards the next goal. It is the journey that counts and, whilst there is a goal in life to pursue, everyone will want to postpone the final destiny. Each step of this way is to be negotiated as a part of a model of relationship between the physicians and the diseased person, that some have called "Personalised Medicine" [234].

Such a strategy calls for a coherent and realistic set of measures of well-being, to assess the disease progression through time and allow accountability, as "one can't improve what can't be measured". This set of studies is aimed at finding some KPIs of that progression, where choice is based on three conditions:

a) that they are relevant to the patient's life, improving his experience of being ill;
b) that they are related to the factors that led to the disease, if possible with a proven epidemiological link or a sound pathophysiological explanation; and
c) that they have impact on the outcomes that are easy to define as disease milestones or catastrophic events that should be avoided or postponed.

These questions were the components of our conceptual research model, that will be discussed in this chapter (***section 5.5.***). Furthermore, building the conceptual model requires the answer to some formulated research questions:

1. Regarding kidney function measurement; which estimated Glomerular Filtration Rate (eGFR) formula is more useful to predict outcomes and correlate with well-being? *(section 5.1.)*
2. How do PROM represent a CKD population? How does a CKD population perform as far as PROM are concerned? *(sections 5.2. and 5.3.)*
3. What is the impact of baseline variables on future endpoints? And how PROM can predict those endpoints? *(section 5.4.)*
4. What are patients' priorities concerning their treatment? What are their preferences regarding what their physicians' first concerns should be? *(section 5.6.)*

The following sections will present discussion regarding these questions.

5.1 Regarding Kidney Function Measurement, Which eGFR Formula is More Useful at Predicting of Outcomes and Correlating with Well-Being?

Being the final pathway of a number of different diseases, CKD behaves very heterogeneously. However, as a disease that is caused by progressive kidney dysfunction, it tends to be analysed through the criterium of residual kidney function, the numerical quantification of which is proportional and roughly equivalent to a percentage of the normal value of GFR. In spite of all the pitfalls with its measurement, it remains the gold standard, and it makes sense: the lower the function, the sicker the patient might be. However, eGFR calculation, thoroughly reviewed in a previous chapter, doesn't guarantee a rigorous quantification of the remaining GFR. Nor does it provide a guide to the complete clinical or biochemical situation for the patient, both at present and for the future.

In this context, our work could demonstrate that:

- There was a high correlation between kidney function assessments by the 4 most published eGFR formulae (CG, MDRD4, MDRD6 and CKD-EPI) regardless of the time points in which they were done ***(tables 11, 12 and 13).***
- Both MDRD4 and MDRD6 formulae returned eGFR values that classify patients in more advanced stages of CKD, as compared to both CG and CKD-EPI formulae. ***(Fig 7)***
- The four eGFR formulae are not good at predicting their own value 24 months later. The higher coefficient of correlation (0.507) between determinations at baseline and at 24 months is given by CG formula. ***(table 15)***
- No correlation could be proved between eGFR measured by any of the four formulae and a set of eleven PROM. ***(table 17)***
- CG formula is the only formula that could predict death within 24 months, with HR coefficient of 0.904 for each 1 mL/min of increase of eGFR. ***(table 23)***
- The four formulae can predict beginning of dialysis within 24 months, with HR coefficients of 0.715 for MDRD4, 0.726 for MDRD6, 0.789 for CG and 0.849 for CKD-EPI formulae for each 1mL/min of increase of eGFR. ***(table 23)***

Our findings reveal that the four formulae are, in fact, measuring the same concept, as they show a high correlation between them.

An interesting point is that more than half the patients who survived 24 months kept the same level of kidney function. This is probably due to the heterogeneity of CKD and censorship of the more diseased patients. Some aetiologies of CKD have a more indolent evolution than others and time imposes a selection that censors the most aggressive. Patients surviving 24 months may not present degradation of kidney function. Also, the control of complications is not the same in all patients. This requires a deeper analysis of other patient's features, namely aetiology of CKD, medication or presence of other known complications, for example albuminuria, to find more useful prognostic clues. In this study, the Charlson Comorbidity Indices were evaluated, as representative of a subject's degree of illnesses, but were not useful to address this question because kidney disease is part of the index, bringing statistic interference.

The fact that the several formulae return different values when used in the same population leads to considerations about bias of age, gender or ethnicity as they present variations in muscular mass, as well as an overestimation up to more than 60% than it may have in advanced kidney disease. This is due to an increased proportion of tubular secretion in relation to the total clearance of creatinine [235].

The lower value returned by MDRD equations had already been reported [88]. This study reported an underestimation of GFR by MDRD equations by 6% in CKD patients and in 29% in healthy people, turning healthy into diseased people, namely the elderly ones. This increase in CKD prevalence, due to overconfidence on MDRD [78], which resulted from the KDOQI guidelines was one of the motivations for this work.

Notwithstanding the accuracy of GFR determination, as kidney disease is a known risk factor for cardiovascular mortality, it would be predictable that there might be a relationship between eGFR and cardiac events in these patients. The advantage of CG formula in predicting mortality that we found has already been presented: Zamora, in 2012 [236], reported that CG formula, compared with MDRD4 and CKD-EPI, was the most accurate for predicting death in ambulatory patients with heart failure. He postulates that the reason for this was the influence of weight, which is both present in the formula and also a risk factor for death in heart failure.

Also, in 2016 [226], the value of several eGFR formulae were tested in different cohorts and concluded that in cohorts with cardiovascular risk, heart failure, and post-myocardial infarction the most accurate formula in predicting cardiovascular mortality was the CG, if calibrated for body surface area, although that relationship was not present in a general population cohort. Four other studies [237-240] reached similar conclusions in post myocardial infarction patients: CG formula is a better predictor of death than the other formulae, as long as it is corrected to body surface.

Reinforcing this controversy, authorities, scientific societies and patients' associations still don't agree on which is the best formula to use: the FDA [241] and the American College of Cardiology [242] recommend the use of CG formula at the bedside. The National Kidney Foundation recommends the MDRD formula [19].

The ability of the 4 studied formulae to predict the results of PROM is worthy of comment: only CG formula could predict the scores of a PROM scale: SPPB, KDQoL_PF and WHODAS. None of the others returned useful results in this context.

Irrespective of the formula used to compute eGFR, one of the goals of medical intervention is preventing the decline of kidney function. Although most of the cited studies agree on the fact that MDRD is more reliable in terms of assessing the true GFR [243], its utility could be greater if it correlated with endpoints. And, as it is a fact that the concept of "healthy start" of RRT exclusively based on eGFR [244-246] is outdated [247], the question about finding an exact number, given by a specific formula, to be used as a KPI of disease progression, loses some importance, because of the importance of the classification stages of the disease. In addition to this is the importance and the interpretation of symptoms, signs and laboratory abnormalities associated with CKD for detection, staging, management (including drug administration) and prognosis. This could be an argument for not having to choose one, as long as the same formula is used throughout time. Yet, the CG formula is simpler and easier to use at the bedside.

Another question of interest is whether a different proportion of each of the several CKD stages in a sample constitutes a potential source of noise in statistical analysis. As there is no clear advantage of one to the others, in our opinion no single eGFR formula seems to deserve to be considered the gold standard, as each one of them has advantages as drawbacks.

Nevertheless, we agree that the search of a better indicator of kidney function than creatinine, with stronger associations with clinical symptoms and adverse outcomes is not over yet and should continue [248].

5.2 How do PROM Represent a CKD Population? How Does a CKD Population Perform as far as PROM are Concerned?

Our CKD population was challenged with some PROM in search for reliable Key Performance Indicators (KPI) of living with kidney disease other than the usual biochemical

and physiological markers. So far, most literature on PROM is reports data on end-stage renal patients, already on dialysis (both peritoneal and haemodialysis) or transplanted, when life is only possible with RRT, therefore introducing a significant interference factor on well-being. This work studied diseased persons without that bias.

5.2.1 Kidney Disease Quality of Life (KDQoL)

As it can be seen in table 28, our patients scored fairly well, in every domain, as compared with other series of CKD patients already on dialysis [249] [250] and with the series of Mujais [196], which also included patients in several CKD stages. They performed better than another study that compared two groups of pre-dialysis CKD patients, divided according to the state of nutrition [197].

Table 28 - KDQoL in several series of CKD patients

	1	2	3a	3b	4	5
	Our Study 2018	Mujais [196] 2009	Campbell [197] 2008		Moura [249] 2014	Lessan-Pezeshki [250] 2009
	Stages III-V (n=60)	Stages III-V (n=1186)	well nourished (n=43)	mal nourished (n=10)	HD (n=322)	HD (n=152)
KDQoL_PF	0.64±0.32	0.56±0.29	0.43±0.28	0.21±0.23	0.44±0.31	0.41±0.30
KDQoL_RP	0.78±0.30	0.50±0.43	0.32±0.39	0.13±0.32	0.27±0.33	0.27±0.32
KDQoL_Pain	0.69±0.35	0.68±0.28	0.67±0.26	0.64±0.33	0.63±0.30	0.49±0.30
KDQoL_GH	0.47±0.19	0.48±0.21	0.42±0.18	0.34±0.14	0.35±0.22	0.39±0.22
KDQoL_MH	0.84±0.20	0.75±0.20	0.71±0.21	0.40±0.23	0.61±0.25	0.49±0.23
KDQoL_RE	0.84±0.27	0.72±0.40	0.63±0.39	0.27±0.41	0.45±0.32	0.35±0.38
KDQoL_SF	0.65±0.26	0.75±0.27	0.72±0.29	0.46±0.33	0.68±0.34	0.45±0.28
KDQoL_VT	0.50±0.25	0.48±0.24	0.42±0.23	0.28±0.26	0.48±0.20	0.39±0.24

(unit avg±sd; range 0-1, in our study there was a small percentage of Stage II patients, according to CG and CKD-EPI)

Figure 12 shows a graphic representation of the averages and standard deviations of the eight domain results presented in table 28. It is interesting to note that our patients performed better in KDQoL_PF, KDQoL_RP, KDQoL_MH and KDQoL_RE, but not so well in KDQoL_Pain, KDQoL_GH, KDQoL_SF, KDQoL_VT, whose scores seem to have been overtaken by both non-dialysis and dialysis patients of other series. This suggests that the

several domains of the KDQoL test evolve separately and argue in favour of an independent analysis of each domain as an autonomous KPI. This supports the theory and aim of this work.

Also, worthy of reference is that fact that in our sample, the median was 100% for two variables (KQQoL_RP and KDQoL_SF) and the 3rd quartile was 100% for three (KQQoL_RP, KDQoL_PF and KDQoL_Pain). These results suggest a "ceiling effect" that may be a drawback to the use of the test in this population, as the variables may not be "selective" enough to untangle subjects with mild disease, not being useful for prognosis at this level of illness. More detailed testing, namely in patients with a "worse" status, is needed to assess the utility of each one of the variables separately, namely the performance of a longitudinal study to access the evolution and, in case of worsening, the steepness of that deterioration.

Considering KDQoL scores for each CKD stage, our patients seem to have better results than Cruz's [251] , who used CG formula to define CKD stages, and have performed similarly in Mujais [196] patients, where there is no mention to the used formula.

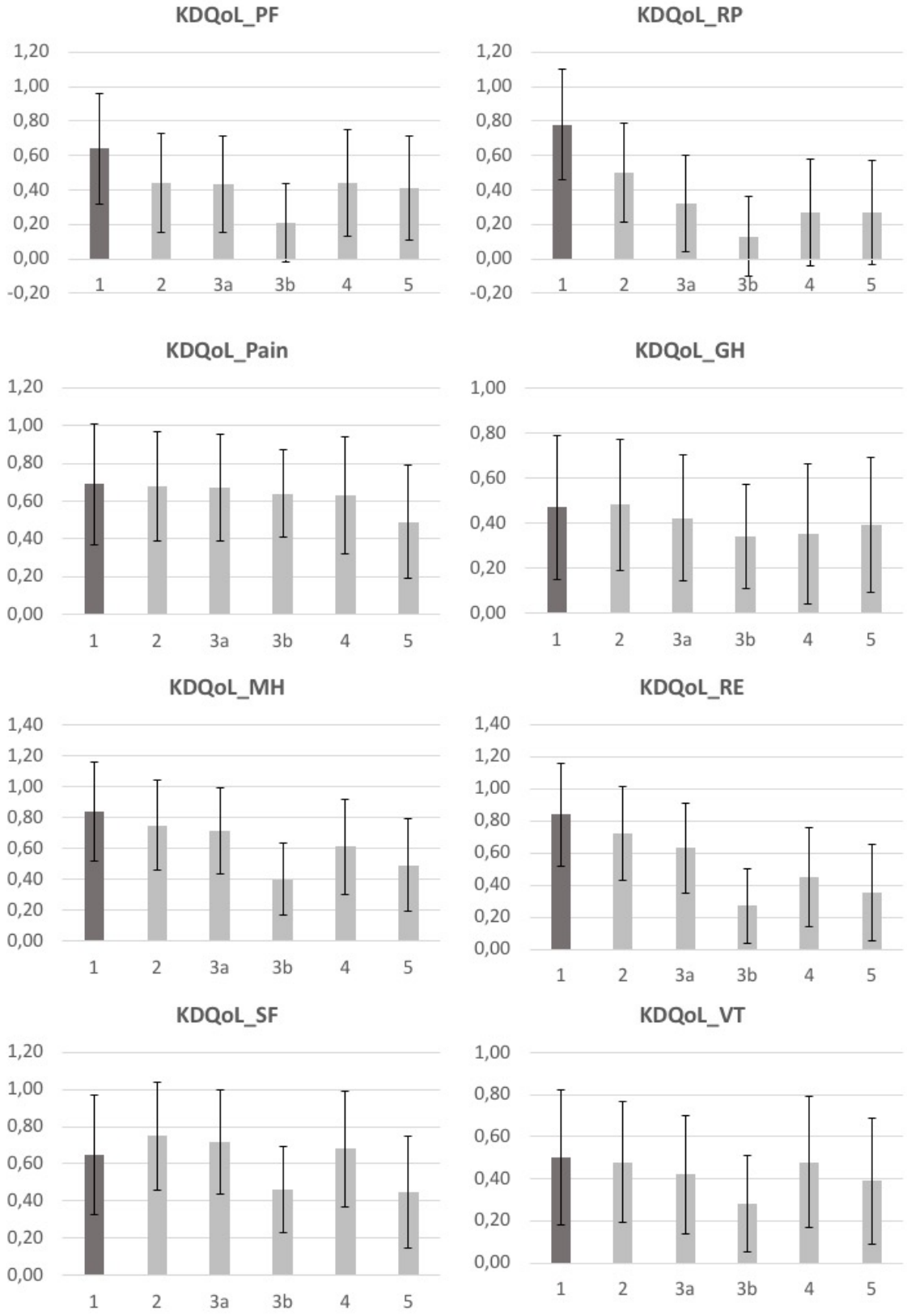


Figure 13 - Mean and standard deviation of the studies mentioned in table 28

(Study numbers are presented in table 28; our study (1) is in darker grey)

5.2.2 World Health Organization Disability Assessment Scale (WHODAS)

When challenged with the WHODAS 2.0, 12-items, our patients scored an average 20±9.8 points, with a range of 12 to 47 in a scale that ranges from 12 (the less disabled patient) to 60 (the most disabled patient). In a 0-100 scale, the average would correspond to a 17% level of disability. However, most patients presented little disability, as the first quartile was 13 points (2% disability), the median 15.5 points (7% disability) and the third quartile 23.25 points (23% disability). We are not aware of published reports of series of non-dialysis CKD to compare with and other series are not directly comparable because of co-variables that may exist. However, some literature can be found regarding other chronic diseases.

Some studies present these results in a range from 0-48 (the punctuation of each question ranges from 0 to 4 points, instead of 1 to 5), which carries some difficulty with directly comparing data. However, if conversion is made to percentages then comparison is easier and results are not very different from other reported work. For example, in a Portuguese population of elderly people in a nursing room an average score of 11.45±11.21 (24% of disability) was presented [252]. Another paper described a chronic population with musculoskeletal pain that had an average score of 25% of disability (no raw scores were published) [253]. Additionally, a survey, carried out in a surgical context [254], reported WHODAS 2.0 results, just before surgery, of 6.6±0.06 (14%), in General Surgery, 9.5±0.08 (20%), in Maxillo-Facial Surgery, 18.8±0.17 (39%), in Plastic Surgery, 20.0±0.12 (42%), in Gynaecologic Surgery and 24.3±0.23 (51%) in Orthopaedic Surgery. In this survey, the results showed significant improvements on these scores after surgery. A fourth paper reported a population in a community rehabilitation clinic with several kinds of deficiencies, in Uganda [255], whose WHODAS 2.0 12-item average score was 12.68±8.3 (27% of disability). There was no information about comorbidities in this work, therefore a more detailed comparison was not possible to carry out.

Another large epidemiologic study made in Taiwan [256], involving more than 100,000 people, ranked several diseases according to their WHODAS 2.0, as follows (all data are

presented as mean percentage points with standard deviations): Dementia (61.42±23.32), Stroke (60.20±23.82), Spinal Cord Injury (55.14±22.61), Depression (43.40±18.60), Bipolar Affective Disorder (40.38±19.87), Schizophrenia (36.4±18.90), Visual Impairment (34.73±20.75), Mental Retardation (34.57±20.32), Autism (33.10±20.15) and Hearing Impairment (25.35±18.44), as compared with "normal"/healthy people who presented an average score of 6.4±8.6. The patients in the work presented here scored better than all groups, except the "normal"/healthy ones. Impairment can be sensory, mental and physical and each one of these vectors is differently affected in each disease context.

5.2.3 Short Physical Performance Battery (SPPB)

The average SPPB score in our sample of patients was 7.4±3.4 (median 8), which corresponds to a 62% of the maximum possible score. A slightly higher result (8.3±2.4; median 9) was reported by Reese [257] in a population of CKD patients with frailty. Another study [258] compared SPPB in two samples of patients, one in Brazil (8.59±2.5) and another in Canada (9.60±2.44), the reported results were similar to this reported in this study. Finally, in another series of elderly patients in the USA [259] the SPPB score was 8.3±2.7. All of them appear to have performed slightly better. Surprisingly, Lattanzio's patients [213] presented, on average, the lowest results (5.2±3.6), in a sample with better average renal function (57 mL/min, using CKD-EPI formula). Although a direct comparison cannot be freely done, the patients in this study performed similarly to those published series, except for the last one.

5.2.4 Satisfaction with Life Scale (SWLS)

To our knowledge, SWLS was also never used in CKD patients before. Our patients scored an average of 25.6±7.5 points and a median of 27, in the range of "high score", well above the neutral 20-point score referred in the instrument. According to the scoring instructions [260], it means that these are "*Individuals who like their lives and feel that things are going well. Of course, their lives are not perfect, but they feel that things are mostly good. Furthermore, just because the person is satisfied does not mean he or she is complacent. In*

fact, growth and challenge might be part of the reason the respondent is satisfied. For most people in this high-scoring range, life is enjoyable, and the major domains of life are going well – work or school, family, friends, leisure, and personal development. The person may draw motivation from the areas of dissatisfaction." This was a surprise for us in a sense that it doesn't fit the general idea that a nephrologist understands from his patients after some years of experience, as many patients complain a great deal during medical appointments, mostly due to subjects not related to health matters.

On the other hand, this general impression of the patient's mood, can be influenced by anticipation of dependence on a machine to live in the near future. This fits from an emotional point of view that is not the focus of this test, as explained earlier [215]. The test doesn't cover this aspect.

Curiously, the patients in this study returned a better result than 33 of the 36 samples of people reported, in many different contexts, some of them referred as healthy in a revision of the instrument, published in 2009 [261]. Moreover, our patients performed better than two published series: one from Spain with Multiple Sclerosis (17.8±7.0) [262] and another from Poland with Breast Cancer (20.67±4.63) [263]. The results were similar to another two series: one also from Spain, representative of the "general" population (24.16±5.73) [264], and another from Sweden with Parkinson Disease (24.2±7.7) [265]. Although the comparison of different diseases at different stages of those diseases is of limited value, it is interesting to verify that a population of CKD is not an outlier both among chronic patients and in "normal" healthy people. Resilience, resistance and coping well are possible weapons to be used to face adversity.

However, deeper psychological evaluation is required before any definite conclusion can be drawn. The SWLS scale claims to be a good predictor of future behaviours such as suicide attempts and to have a high correlation with a life satisfaction component of subjective well-being. We didn't look for depression in this study, so there might perhaps be a bias of selection, as some elderly people with depression refused to participate in the study. Therefore, without a context of depression, these results are not encouraging for the usage of this test for the evaluating CKD patients as a general screening or follow-up test.

5.2.5 Correlation Between Several PROM

As far as we know, many of these testes were never used together. Consequently, there is no record of relationships between them. However, it is interesting to observe significant correlations between the several PROM tests **(table 19)**.

- The strongest correlations occur between physical related scales: SPPB, WHODAS and KDQoL_PF.
- The most transversal domain was KDQoL_VT. This domain has shown significant correlation with all but two tests: the KDQoL_SF and KDQoL_GH. The first, as already discussed, is the most problematic as representative of the claimed construct.
- On the other side, KDQoL_GH has no correlation with any of the others. In fact, this domain is probably so non-specific that no other factor correlates significantly with it. Also, it also has shown a borderline internal consistency and many not be representing the construct it was meant to.
- It is also noteworthy that the domains that have a bigger contribution to the Physical Component Summary (KDQoL_PF, KDQoL_RP, KDQoL_Pain and KDQoL_GH) have few (only two in six possible) and weak correlations. Also Walker [266] has found a correlation between CKD and physical disability.
- The major components of the Mental Component Summary of KDQoL return more significant correlations, both in number (3 out of 5) and in strength. KDQoL_SF was not considered.
- There are also some significant correlations between domains across summary components. The highest is between KDQoL_PF and KDQoL_VT, but some others (6 out of 12 possible) can be noted.
- SWLS has shown only two significant correlations: KDQoL "Mental Health" and "Energy/Fatigue", both belonging to the Mental Component Summary of KDQoL.
- SPPB correlates with all but two tests: SWLS and KDQoL_GH. A Portuguese study designed to validate KDQoL domains and ESRD-specific variables, failed to

correlate the construct "Satisfaction of the Patient" with any of the 8 KDQoL domains, which did not happen with other variables [221].

- WHODAS correlates with 2 scales of the Physical Component Summary (KDQoL_PF and KDQoL_RP) and another 2 of the Mental Component Summary (KDQoL_VT and KDQoL_MH)

These findings suggest a clustering of the tests according to the summary measures of KDQoL which, to be confirmed, seem to have a higher association for mental domains. Though, this division between physical and mental components is interesting but our data cannot confirm this hypothesis.

5.3 What Are the Most Important Predictors of PROM in a CKD population?

5.3.1 Kidney Disease Quality of Life (KDQoL)

Several predictive relationships were found between baseline variables and KDQoL domains scores *(table 20)*:

- KDQoL_PF is positively influenced by male gender, labour situation active, higher education, and negatively influenced by older age, higher comorbidity index (both scales) and decreasing eGFR (only CG formula).
- The only influence that could be found on KDQoL_RP was negative, by higher comorbidity index (with 1987 scale).
- The only influence that could be found on KDQoL_VT was negative, by higher comorbidity index (with 1987 scale).
- KDQoL_RE is positively influenced by male gender, labour situation active, and negatively influenced by older age.
- None of the studied variables demonstrated any influence on KDQoL_Pain, KDQoL_GH, KDQoL_MH and KDQoL_SF.

In his paper involving 1186 patients, Mujais [196] demonstrated that the level of kidney function had a similar effect on scores of KDQoL_PF and KDQoL_MH, as ours, but also on KDQoL_PF, KDQoL_GH, and KDQoL_RE and KDQoL_SF, which our study didn't show. Neither study could demonstrate a relationship between kidney function and domains KDQoL_Pain and KDQoL_VT. No mention is made regarding the formula that was used to estimate GFR. The differences between results may also be due to different sizes of series. Campbell [197] demonstrated the effect of nutritional state on the scores of all domains, except pain, in a CKD population. Also Miskulin [267] has compared Autosomal Dominant Polycystic Kidney Disease with CKD patients with their counterparts with the same level of kidney function from the general population. They found that KDQoL scores of patients with lower renal function (GFR 20-44 mL/min) were lower for several domains: KDQoL_PF, KDQoL_RP, and KDQoL_GH, and KDQoL_VT. They also found that those scores in patients with GFR above 45 mL/min were at least the same as their age matched general population in all but KDQoL_GH domain. This reinforces the statement that QoL in earlier stages of CKD is not worse than that in healthy people.

In summary, there seems to be no question as to whether worsening of kidney function is an important determinant of KDQoL scores, although there isn't a consensus on the real impact on each of the domains, as it varies from sample to sample. This is compatible with the heterogenicity of CKD itself.

5.3.2 World Health Organization Disability Assessment Scale (WHODAS)

In our patients, the WHODAS is negatively influenced by female gender, retired labour situation, by higher comorbidity index (only demonstrated with 1987 scale), by older age and by decreasing eGFR (only when computed by CG).

This is in accordance with a Taiwanese study [256], which also reached similar conclusions: women, elderly and poorer populations are affected disproportionally by disability. Another paper [268] analysed disability in diabetic patients and found that depression, especially severe, frequency of exercise, number of diabetic complications, severity of diabetes, and extent of chronic comorbidities were the factors with a significant

influence on higher WHODAS 2.0 scores, expressing more disability. It is also in accordance with our findings, as CKD is also an important complication of diabetes.

5.3.3 Short Physical Performance Battery (SPPB)

SPPB in our population was positively influenced by higher education, by labour (employment) situation "active" and negatively influenced by older age, higher comorbidity index (both scales) and decreasing eGFR (only when computed by the CG formula).

Our search in literature found some interesting data: Reese [257] reported the negative influence of frailty and decreased GFR on physical performance, as expressed by SPPB results. Also, Lattanzio [213], in her paper about physical performance and hospitalization, reported that SPPB is dependent on GFR, on age, albumin level, mental state, comorbidities, level of autonomy, and antecedents of stroke. The overall direction of these findings is the same as ours.

5.3.4 Satisfaction with Life Scale (SWLS)

None of the studied variables demonstrated any influence on the SWLS scale. In fact, this test was developed to represent individual assessment of one's global judgement of life. It is an intellectual procedure, dependant on both affective and cognitive mechanisms that affect subjective well-being and it may be influenced by factors other than disease, mainly related to life expectations, positive/negative affect, self-esteem, optimism or pessimism, perceived stress, or suicide ideation [269]. We didn't cover depression within the scope of this work, so this test probably is not useful as an exploratory work or follow-up test without that context. Therefore, no utility of this scale for this context cold be proven in this study.

5.4 What is the Impact of Baseline Variables on Future Endpoints and How PROM can Predict Those Endpoints?

Although a relatively small sample size was used in this study our data can confirm that some PROM predict "hard" outcomes ***(Table 24):***

- Lower scores of SPPB predict risk of death, beginning of dialysis and hospital admissions within 24 months.
- Higher scores of WHODAS (the more disabled patients) predict risk of death and beginning of dialysis within 24 months.
- Lower scores of KDQoL_PF predict risk of death and hospital admissions.
- Lower scores of KDQoL_RP predict risk of beginning of dialysis within 24 months.
- Lower scores of KDQoL_VT predict risk of hospital admissions within 24 months.
- Lower scores of KDQoL_RE predict risk of hospital admissions within 24 months.
- Lower scores of KDQoL_MH predict risk of hospital admissions and usage of emergency services.
- No predictive value could be found for SWLS, KDQoL_Pain, KDQoL_GH and KDQoL_SF.

These results are comparable to published series. Volpato [270] reported that the SPPB score at discharge from hospitalization due to congestive heart failure, pneumonia, chronic obstructive pulmonary disease, or minor stroke correlated negatively with rate of decline in activity of daily living performance over the follow-up and that early decline in SPPB had a steeper increase in activity of daily living difficulty and higher risk of rehospitalization or death over the next year. Guralnik found that SPPB can predict future disability [271] and mortality [172]. Pennix [272] found a correlation between low score SPPB and hospitalization in non-disabled old people.

Lee [273] has shown that WHODAS is a good predictor to return to work for patients with head and neck cancer.

Dialysis Outcomes Practice Patterns Study (DOPPS), a very large study involving 17,236 patients in 7 countries, found a correlation between all the 8 domains of KDQoL and

both mortality and hospitalization [274]. Hall [191] correlated KDQoL scores with mortality and hospitalizations.

Moreover, the confirmation of these relationships between some PROM and certain endpoints, supports new approaches, assuming different strategies and aiming directly at improving PROM scores as surrogates of future outcomes. For example, one important determinant of QoL, already known, is anaemia, which has a significant impact on hospitalizations [275 276]. Hansen [277] proved that it is possible, not only to improve outcomes, decreasing hospitalizations, but also to improve scores of KDQoL, when anaemia is treated. This same rationale can be applied to other situations in which there is a slow response to medical decisions: the result of the decision could be guided by the PROM; provided that it is proven that it has impact on the desired endpoint.

5.5 What Are Patients' Priorities Concerning Their Treatment? What Are Their Preferences Regarding What Their Physicians First Concerns Should Be?

The general hierarchy for the preferences of our patients of his/her physician's priority was:

- Avoiding death
- Avoiding dialysis = Avoiding worsening of laboratory results
- Avoiding worsening of general health = Avoiding hospitalisations
- Avoiding ER usage.

Overall, 61% of the patients, have chosen "Avoid death" as first option. The option, "Avoid Dialysis" was also chosen as second option by 39% and as third option by 30.5% of the patients. The alternative "Avoid worsening of lab tests" was chosen by 33.9% as third option and by 30.5% as fourth option. "Avoid worsening of general health", was the option in which there was greater dispersion of results: 22.0% as fourth and sixth preference, 18.5% as second and third option. It is possible that this dispersion is due to the difficulty of defining it, as it is the least measurable alternative. "Avoid hospital admissions" was placed in fourth

place, as well as fifth places by 33.9% of patients each. Finally, "Avoid ER episodes" was the lowest ranked alternative; being classified in fifth place by 33.9% and in sixth place by 32.2% of the patients.

The increasing variation coefficient from the first to last choice is in line with the difficulty in answering this question with a Likert scale that the patients have shown at the beginning. This method of defining the hierarchy of patients' preferences uncovers that people are sure of their first preferences, but not so sure about the following ones. The method we used has the advantage of avoiding neutrality, because it demands an answer to the question, rather than a defensive "middle option". It returns an ordinal variable which as a result can then be analysed the same way as the result of the Likert scale. It may have the inconvenience of being one sided, because it only gives the order of options from the most wanted to the least wanted, rather than the result variable of the Likert scale, which can have two directions (either from the neutral position to positive – "most wanted", and to the negative position – "most hated"), but this was not relevant for this particular study.

The endpoint "death" is still the most valued by patients, it was the only one that more than half of the preferences assigned a defined rank. This confirms that it is the most valued endpoint to follow. This is true in spite of the drawbacks already mentioned, which were the motivation for this work. It further reinforces the need that any future surrogate endpoints to be adopted must be able to anticipate this one, to be of value in the clinical or research context.

The case of "Avoiding worsening of general health", being the one with most disparity of results confirms that the lack of an objective definition makes it vague and reinforces the need of validated tangible indicators when it comes to defining surrogate outcomes to guide medical practice or clinical research. On the other hand, options that got a higher rank seem to be the ones that patients really appreciate: "avoid death", "avoid dialysis" and "avoid worsening of lab tests".

Moreover, there seems to be a tie between "Avoiding worsening of general health" and "Avoid hospital admissions", in more educated, retired, over 65 and men. This may be interpreted in two ways: either they don't separate both situations, or they consider that the physicians cannot avoid it.

An interesting finding was the relative low importance that patients gave to the usage of medical services, both hospitalization and emergency services. These endpoints were included in the model as surrogates of bad health. At this point, it is our belief that many of them did not understand the question the same way. This is particularly true for poorer and less educated patients. This last group used emergency services 2.578-fold more than their more educated counterparts. Opposite to the intention of the study, it may be possible that for some patients the utilization of medical services was not perceived as a surrogate of bad quality of life. Probably they face those choices as solutions, rather than proxies of their health problems and understand that therefore it is not their physician's obligation to avoid the utilization of medical services.

As expected, all groups gave higher scores to "Avoid Hospitalizations" than "Avoid ER Services". This last option is consistently the one with fewer points, meaning that they want to avoid a hospitalization if they can solve their problem in ambulatory.

The apparent tie between "Avoiding dialysis" and "Avoiding worsening of lab tests" also deserves a commentary. Men and poorer patients gave them a tie. All the other groups appreciated not beginning dialysis over not worsening laboratory tests. Moreover, one problem of CKD is that it is an asymptomatic condition until the later stages, with too much importance being given to laboratory tests. Some patients can understand that this is a limitation and is the only data that physicians have to follow-up with them, but it may be possible that some think that laboratory tests are the key to their recovery.

This is a field that requires more research. The concepts of preferences and patient's needs and their preferences must be dealt together because they are related. There is a large clinical trial ongoing to understand the expectations and priorities of elderly patients for a first medical treatment for cancer (PRIORITY Study) [278]. Recruitment is ongoing until 2020. It will evaluate the opinion of patients regarding these issues not only at the beginning of treatment, but also over time, giving a longitudinal picture of patients' performance. Patients with CKD would benefit from a similar study.

5.6 Qualitative Appraisal of the Proposed Conceptual Model of Relationships Between Predictors, PROM and Endpoints

Gathering all data, it becomes clear that some relationships between studied predictors and chosen endpoints are in accordance with the proposed conceptual model. According to this model, a given PROM would be influenced by one or more predictors and transmit that significance to a particular endpoint and serve as a surrogate for it. Eleven PROM were studied and challenged with 11 variables as justification. Four endpoints were considered.

Tables 29 through 32 show the significant relationships that could be found between predictors, PROM and endpoints. On the top line of each table, predictor variables are presented: gender, age, yearly income, labour situation, schooling, comorbidities (by both scales, 1987 and 2011) and estimated GFR (computed by four formulae). On the left column, endpoints (in bold) and significant PROM are presented. Numbers enhanced in orange are the significant univariate linear regression coefficients between predictors and PROM. Numbers highlighted in blue are the hazards ratios of predictive value of PROM to endpoints. Finally, the numbers in green represent the hazards ratio of predictive value of predictors to endpoints. Empty cells represent non-significant statistic relationships. For the sake of simplicity, for each endpoint, when a given PROM had significant value to show, that line was erased. Sub-titles under the tables mention PROM whose lines were erased.

Table 29 - Conceptual Model for Endpoint "Death within 24 months"

	Predictive value of PROM to Endpoint	Gender Male	Age	Income <7000€/y	Labour Situation Retired	Schooling <Primary	Charlson 1987	Charlson 2011	eGFR CG	eGFR CKD-EPI	eGFR MDRD4	eGFR MDRD6
Mortality			HR: 1.139	HR: 5.071		HR: 4.312	HR: 1.416	HR: 1.236	HR: 0.904			
SPPB	HR: 0.761		-0.154		-3.828	-2.812	-0.826	-0.342	0.083			
WHODAS	HR: 1.088	-6.039	0.361		7.774		1.980		-0.224			
KDQoL_PF	HR: 0.075	0.213	-0.015		-0.302	-0.300	-0.081	-0.032	0.008			
KDQoL_VT							-0.034					
KDQoL_RE	HR: 0.071				-0.157							
KDQoL_RP							-0.032					

(SWLS, KDQoL_Pain, KDQoL_GH, KDQoL_SF, and KDQoL_HM have shown no utility for this concept model regarding this endpoint)

Table 30 - Conceptual Model for Endpoint "Dialysis within 24 months"

	Predictive value of PROM to Endpoint	Gender Male	Age	Income <7000€/y	Labour Situation Retired	Schooling <Primary	Charlson 1987	Charlson 2011	eGFR CG	eGFR CKD-EPI	eGFR MDRD4	eGFR MDRD6
Dialysis								HR: 1.168	HR: 0.789	HR: 0.849	HR: 0.715	HR: 0.726
SPPB	HR: 0.824		-0.154		-3.828	-2.812	-0.826	-0.342	0.083			
WHODAS	HR: 1.052	-6.039	0.361		7.774		1.980		-0.224			
KDQoL_PF		0.213	-0.015		-0.302	-0.300	-0.081	-0.032	0.008			
KDQoL_VT							-0.034					
KDQoL_RE					-0.157							
KDQoL_RP	HR: 0.137						-0.032					
KDQoL_MH												

(SWLS, KDQoL_Pain, KDQoL_GH, KDQoL_SF, and KDQoL_HM have shown no utility for this concept model regarding this endpoint)

Table 31 - Conceptual Model for Endpoint "Hospital Admissions within 24 months"

	Predictive value of PROM to Endpoint	Gender Male	Age	Income <7000€/y	Labour Situation Retired	Schooling <Primary	Charlson 1987	Charlson 2011	eGFR CG	eGFR CKD-EPI	eGFR MDRD4	eGFR MDRD6
Hospital Admissions							HR: 1.290	HR: 1.245				
SPPB	HR: 0.833		-0.154		-3.828	-2.812	-0.826	-0.342	0.083			
WHODAS		-6.039	0.361		7.774		1.980		-0.224			
KDQoL_PF	HR: 0.172	0.213	-0.015		-0.302	-0.300	-0.081	-0.032	0.008			
KDQoL_VT	HR: 0.029						-0.034					
KDQoL_RE					-0.157							
KDQoL_RP							-0.032					
KDQoL_MH	HR: 0.106											

(SWLS, KDQoL_Pain, KDQoL_GH and KDQoL_SF, have shown no utility for this concept model regarding this endpoint)

Table 32 - Conceptual Model for Endpoint "ER utilization within 24 months"

	Predictive value of PROM to Endpoint	Gender Male	Age	Income <7000€/y	Labour Situation Retired	Schooling <Primary	Charlson 1987	Charlson 2011	eGFR CG	eGFR CKD-EPI	eGFR MDRD4	eGFR MDRD6
ER episodes						HR: 2.578		HR: 1.153				
SPPB			-0.154		-3.828	-2.812	-0.826	-0.342	0.083			
WHODAS		-6.039	0.361		7.774		1.980		-0.224			
KDQoL_PF		0.213	-0.015		-0.302	-0.300	-0.081	-0.032	0.008			
KDQoL_VT							-0.034					
KDQoL_RE					-0.157							
KDQoL_RP							-0.032					
KDQoL_MH	HR: 0.234											

(SWLS, KDQoL_Pain, KDQoL_GH and KDQoL_SF, have shown no utility for this concept model regarding this endpoint)

Figure 14: presents the schematic representation of all possible relationships between Predictors, PROM and Endpoints, according to the proposed conceptual model. It is divided into 8 schemes, designated alphabetically from A to H, each representing different meaning and utility of the PROM in a given situation.

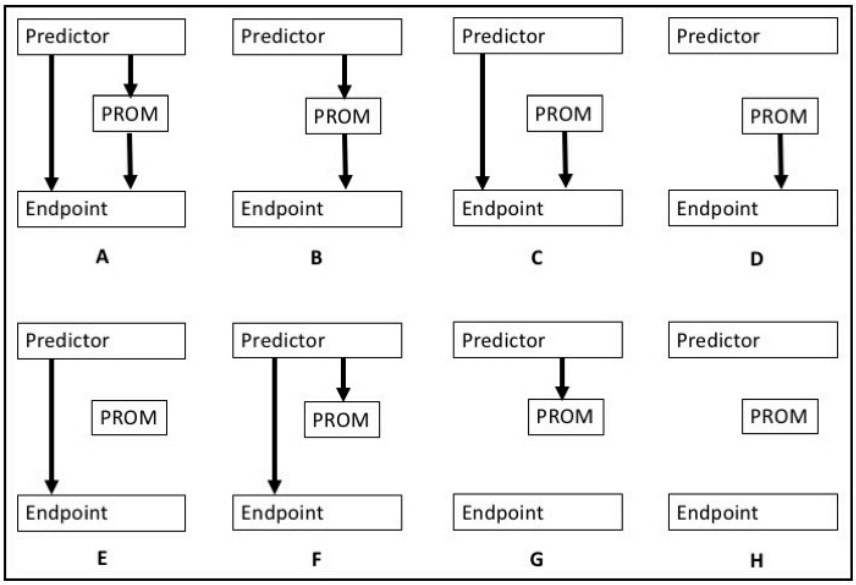


Figure 14 - Map of all possible relationships of the proposed conceptual model

(Arrows represent significant relationships between predictors, PROM and endpoints)

Scheme A is the one that fulfils the whole model: for these cases, it was possible to prove that a given predictor had influence on both a PROM and on an Endpoint, and, at the same time, that PROM could predict the same Endpoint. It means that the PROM carries the influence that the predictor has on that endpoint. This qualifies these PROM to become useful for daily use in clinical context because there is a known justification for the predictive capacity of the PROM. Examples of these situations are shown in table 33:

Table 33 - Predictors, PROM and Endpoint fulfilling the proposed conceptual model

Predictors	PROM	Endpoints
Age, Schooling, Comorbidities (both scales), eGFR (only GC formula)	KDQoL_PF	Mortality
Comorbidities (both scales)	KDQoL_PF	Hospital Admissions
Age	KDQoL_RE	Mortality
Comorbidities (only 1987 scale)	KDQoL_VT	Hospital Admissions
Age, Schooling, Comorbidities (both scales), eGFR (only GC formula)	SPPB	Mortality
Comorbidities (only 2011 scale), eGFR (only CG formula)	SPPB	Dialysis
Comorbidities (both scales)	SPPB	Hospital Admissions
Age, Comorbidities (only 1987 scale), eGFR (only CG formula)	WHODAS	Mortality
eGFR (only CG formula)	WHODAS	Dialysis

In a number of cases, represented in ***scheme B***, predictors have influence on PROM and PROM can predict endpoints, but there is no relationship between predictors and endpoints. In these cases, these PROM can be used as surrogate of endpoints, but they cannot claim to be representative of those predictors and other causes of that capacity must be sought. These are listed in table 34.

Table 34 - Predictors predict PROM, PROM predict Endpoints, Predictors do not predict Endpoints

Predictor	PROM	Endpoint
Comorbidities (only 1987 scale)	KDQoL_RP	Dialysis
Age, Labour Situation, Schooling, Comorbidities (only 1987 scale)	SPPB	Dialysis
Gender, Age, Labour Situation, Comorbidities (only 1987 scale)	WHODAS	Dialysis
Gender, Age, Labour Situation, Schooling, eGFR(CG)	KDQoL_PF	Hospital Admissions
Age, Labour Situation, Schooling, eGFR (CG)	SPPB	Hospital Admissions
Gender, Labour Situation	KDQoL_PF	Mortality
Gender, Labour Situation	KDQoL_RE	Mortality
Labour Situation	SPPB	Mortality
Gender, Labour Situation	WHODAS	Mortality

In a third group, depicted in ***scheme C***, there is no relationship between predictors and PROM, but there is a predictive relation between PROM and endpoints, as well as between predictors and endpoints. In these situations, PROM can be used as surrogate of endpoints, but they do not express the relationship of those predictors on endpoints. These are shown in table 35.

Table 35 - Predictors and PROM predict Endpoints, but Predictors do not predict PROM

Predictors	PROM	Endpoints
Income	SPPB	Mortality
Schooling, Income, Comorbidity (only 2011 scale)	WHODAS	Mortality
Income	KDQOL_PF	Mortality
Schooling, Income, Comorbidity (both scales), eGFR (CG)	KDQOL_RE	Mortality
eGFR (MDRD4, MDRD6 and CKD-EPI)	SPPB	Dialysis
eGFR (MDRD4, MDRD6 and CKD-EPI)	WHODAS	Dialysis
eGFR (all formulae)	KDQOL_RP	Dialysis
Comorbidity (only 2011 scale)	KDQOL_VT	Hospital admissions
Comorbidity (only 2011 scale)	KDQOL_MH	Hospital admissions

A fourth group, charted in ***scheme D***, includes PROM that can predict endpoints, but do not reflect the influence of the studied variables as predictors. In these cases, PROM are expressing some other background other than the variables of the proposed conceptual model. This is shown in table 36.

Table 36 - PROM predict Endpoints, but Predictors do not predict neither PROM nor Endpoints

PROM	Endpoint	Predictors not represented
SPPB	Mortality	Gender, eGFR (MDRD4, MDRD6 and CKD-EPI formulae)
WHODAS	Mortality	eGFR (MDRD4, MDRD6 and CKD-EPI formulae)
KDQoL_PF	Mortality	eGFR (MDRD4, MDRD6 and CKD-EPI formulae)
KDQoL_RE	Mortality	eGFR (MDRD4, MDRD6 and CKD-EPI formulae)
SPPB	Dialysis	Gender, Income
WHODAS	Dialysis	Schooling, Income, Comorbidity (only 2011 scale)
KDQoL_RP	Dialysis	Age, Gender, Schooling, Labour Situation, Income, Comorbidity (only 2011 scale)
SPPB	Hospital Admissions	Gender, Income, eGFR (MDRD4, MDRD6 and CKD-EPI formulae)
KDQoL_PF	Hospital Admissions	Income, eGFR (MDRD4, MDRD6 and CKD-EPI formulae)
KDQoL_VT	Hospital Admissions	Age, Gender, Schooling, Labour Situation, Income, eGFR (all formulae)
KDQoL_MH	Hospital Admissions	Age, Gender, Schooling, Labour Situation, Income, Comorbidities (only 1987 scale), eGFR (all formulae)

After the upper row, which confirms PROM as useful, according to the proposed conceptual model, the lower row also shows some relationships between predictors, PROM and endpoints which do not fit the model but, nevertheless, they are worthy be looked at.

Scheme E applies to situations in where there is no relationship involving PROM, while keeping relationships between predictors and endpoints. Although this relationship exists, no PROM of our conceptual model has proven to be useful to express it.

In another group, outlined in ***scheme F***, there is a significant relationship between predictors and PROM, also between predictors and endpoints, but no relation between PROM and endpoints. In these situations, PROM are not useful as surrogates of endpoints, although they bring the influence of those predictors.

In some of other cases, predictors can predict PROM, but have no other relationship in the model. In these cases, the utility of PROM is limited to representing the predictors with no prognostic value, as far as these endpoints are related. In these cases, PROM are representative of predictors, but no conclusion to the future can be proposed. They are represented by ***scheme G***.

Finally, ***scheme H*** is representative of those hypotheses of relationships of the proposed model that could not be confirmed at all. PROM involved in these hypothetic relationships may not be helpful. In other words, although their intrinsic value remains intact, they are not useful as KPI in the context of the patients studied in this work, with those predictors and endpoints. Four scales and domains presented no relationship either with studied PROM and with endpoints: SWLS, KDQoL_Pain, KDQoL_GH and KDQoL_SF.

6 Conclusions and Future Work

A common flaw in the management of a chronic disease, namely Chronic Kidney Disease (CKD) is the lack of consistency between clinical data, including laboratory tests, and the patient's experience of being ill. Since this disease is asymptomatic until late stages, the physician is usually guided by available data derived from laboratory tests and physical examination, which supports his prescriptions and advice. However, often, these numbers fail to show a close connection with the patient's real status, especially as far as prognosis is concerned.

The goal of this work was to search for Key Performance Indicators (KPI) which might be indicators of disease other than the usual clinical data and laboratory tests in CKD. Those indicators should express the experience of living with the disease. They would have to have a significant link to both a set of pre-existing variables and to endpoints that are relevant to the patients. They could then be targeted for intervention, as their improvement would lead to a better management of living with the disease. In addition, we aimed to compare both comorbidities indices and eGFR formulae in a well-being perspective, finding out which of these available indices would be more useful in predicting the endpoints that are most relevant to patients.

In chapter 2, a contextualization of the disease is made, presenting key definitions, mechanisms of disease, epidemiology, causes, pathophysiology, natural history and diagnosis, with a special emphasis on the difficulties of measuring kidney function. Also, we present an extensive list of the standard indicators that reflect the mechanistic perspective that often drives physicians' decisions.

Broadening the scope of the problem, a general approach to chronic diseases is presented in chapter 3, highlighting models of interventions, both at the individual and organizational levels. Some existing indicators are also covered, together with the contexts in which they are commonly used.

For that exploration, we conducted an observational study and recruited 60 patients with Chronic Kidney Disease to whom questionnaires of Performance (Short Physical Performance Battery), Disability (World Health Organization Disability Assessment

Schedule), Satisfaction with Life and Health Related Quality of Life (Kidney Disease Quality of Life) were administered. These tests are generally called Patient Reported Outcome Measures (PROM). The description of the experimental work and its results is presented in chapter 4.

Our hypothesis was based on a conceptual model which postulated that a given PROM would be suitable for daily use in clinical context provided that it met 3 conditions: a) that it had significant predictive capacity of a given endpoint; b) that any baseline variable that was predictive of that PROM also had prognostic ability of the same endpoint of which the PROM proved to be predictor; c) that its determination is simple enough to be used in clinical context, as part of a medical appointment. That specific PROM would have the ability to link Predictors with PROM and Endpoints with statistically significant relationships. We tested 11 PROM against 11 baseline variables and 4 endpoints.

As predictors, we have selected Demographic Data (gender, age, education, income and labour situation), Comorbidity indices (using the original Charlson's 1987 scale and a newer, published in 2011), estimations of Glomerular Filtration Rate (GFR), comparing the 4 most published formulae: Cockcroft-Gault, MDRD with 4 and 6 variables and CKD-EPI) and untoward health events of the previous year. As relevant endpoints, we have chosen death, time to chronic dialysis, hospital admissions and emergency services utilization. The follow-up period was 24 months.

Two years later, patients were checked to see if they were either still alive; if had undergone renal replacement therapy in the form of haemodialysis or peritoneal dialysis and if they had been hospitalized or used emergency services. In addition, their kidney function was checked at two time points: 12 and 24 months following their use of the questionnaires.

Lastly, we wanted to order the relevancy of the endpoints to the patients. For that, they were asked to rank six endpoints according to what they think should be their physician's priority (avoid death, avoid dialysis, avoid worsening of laboratory tests, prevent further deterioration of medical condition, avoid hospital admissions and avoid emergency episodes).

Notwithstanding the small sample size, this study provides useful insights into a number of important questions:

A. Concerning usefulness of PROM:

1. Short Physical Performance Battery (***SPPB***) can predict death, dialysis and hospital admissions within 24 months. Related to its capability of predicting death, it is influenced by age, education, comorbidities (by both scales tested) and eGFR (only according to CG formula). Concerning prediction of dialysis, it carries the influence of comorbidities (only by 1987 index) and eGFR (only according to CG formula). Regarding prediction of hospital admissions, it represents both scales of comorbidities.
2. Disability, as quantified by the World Health Organization Disability Assessment Schedule (***WHODAS***) 2.0 12-items test, can predict death and dialysis within 24 months. Connected to prediction of death, it carries the influence of age, comorbidities (only by 1987 index) and eGFR (only according to CG formula). The ability to forecast dialysis is influenced by eGFR (only according to CG formula).
3. Physical Functioning domain of Kidney Disease Quality of Life (***KDQoL_PF***) can predict death and hospital admissions within 24 months. In relation to death, the involved predictors are age, education, comorbidities (both scales) and eGFR (only according to CG formula). Connected to hospital admissions, we have found both scales of comorbidities.
4. Role Emotional domain of Kidney Disease Quality of Life (***KDQoL_RE***) can predict death within 24 months. It reflects the influence of age.
5. Energy/Vitality domain of Kidney Disease Quality of Life (***KDQoL_VT***) can predict hospital admissions within 24 months, expressing the influence of comorbidities (by both scales)
6. Role Physical domain of Kidney Disease Quality of Life (***KDQoL_RP***) can predict dialysis within 24 months, but none of the variables of our model could explain this relationship.

7. Mental Health domain of Kidney Disease Quality of Life (***KDQoL_MH***) can predict hospital admissions and ER utilization within 24 months, but none of the variables of our model could explain this relationship.
8. Pain, Social Function and General Health domains of Kidney Disease Quality of Life (***KDQoL_Pain***, ***KDQoL_SF*** and ***KDQoL_GH***), as well as the Satisfaction With Life Scale (***SWLS***) were not found to be useful in predicting any of the proposed endpoints, in the context or our patients. The particular case of domain KDQoL_SF has shown little internal consistency, in line with other Portuguese language papers. This suggests that it may be the weakest scale of the test and, as this doesn't happen in the original language there may be a problem with translation.

B. Concerning the measurement of kidney function:

9. The Cockcroft-Gault formula to compute estimated GFR is the only that can predict mortality within 24 months.
10. All eGFR formulae could predict beginning of dialysis.
11. Only the Cockcroft-Gault formula could predict the scores of PROM scales: Short Physical Performance Battery, Physical Function domain of Kidney Disease Quality of Life short form and World Health Organization Disability Assessment Schedule 2.0.

C. Concerning comorbidity assessment:

12. Both the Charlson comorbidity scales (1987 and 2011) are useful for the prediction of studied endpoints. The 1987 formula predicts death and hospital admissions, while the 2011 formula is more comprehensive, with the ability to predict mortality, dialysis, hospital admissions and emergency episodes.

D. Concerning preferences of patients

13. The highest priority of patients is that their physician's main concern should be to "Avoid death". The options "Avoid dialysis" and "Avoid worsening of lab tests"

come next, in a tie. This was roughly reproduced in every sub-group. Thus, these are the distal endpoints that, in the absence of closer ones, should continue to guide medical practice, clinical research and accountability in health management.

14. Patients seem to consider health services a benefit, rather than surrogates of bad health, as they ranked "Avoid hospitalization" and "Avoid emergency episodes" in the last places, after all the others, including "Avoid worsening of general health".

E. Concerning the proposed conceptual model

15. Eight possible schemes were drawn from the analysis. The first four have shown to have clinical utility.

- The most significant and useful is ***scheme A***, in which a given predictor had influence on both a PROM and on an Endpoint, and, at the same time, that that PROM could predict the same Endpoint. It means that the PROM carries the influence that the predictor has on that endpoint.
- In ***scheme B***, predictors have influence on PROM and PROM can predict endpoints, but there is no relationship between predictors and endpoints. n these cases, these PROM can be used as surrogate of endpoints, but they cannot claim to be representative of those predictors and other causes of that capacity must be sought.
- In ***scheme C***, there is no relationship between predictors and PROM, but there is a predictive relation between PROM and endpoints, as well as between predictors and endpoints. In these situations, PROM can be used as surrogate of endpoints, but they do not express the relationship of those predictors on endpoints.
- In ***scheme D***, PROM can predict endpoints, but do not reflect the influence of the studied variables as predictors. In these cases, PROM are expressing some other background other than the variables of the proposed conceptual model.

- In ***schemes E through H*** it was not possible to find predictive capacity of PROM and thus they cannot be considered useful for usage in this clinical context. Four scales and domains presented no relationship either with studied PROM and with endpoints: SWLS, KDQoL_Pain, KDQoL_GH and KDQoL_SF.

There is a new paradigm of health care. Volume of services is being replaced by delivery of value to the patient and the society. In this context, value is the relationship between the outcomes and the costs. So far, they have been analysed separately, mostly due to lack of standardization. The pressure to reduce costs demands that outcomes become tangible. Death is the most used outcome, both in clinical and in research contexts and everyone's mindset is tuned to it, as our study of patients' preferences has shown, understandably so. However, as everyone will eventually die, death can only be postponed and thrown out of the observational period. Focusing on death as the main outcome will not change patients' experience of being ill. Giving priority to this experience is the difference between excellent and good care. However, existing outcomes have been developed by medical specialities within hospital and physician-centred models of care. It is time to reinforce work related to on patient-centred frameworks of outcomes that give priority to patients' needs, rather than focusing on postponing death or other catastrophic events. The development of strong measures of outcomes reported by patients is a good path to follow. The ambition of this exploratory work is to have added something to the construction of that model.

One limitation of this study is the reduced sample size. However, the recruitment difficulties, which had already been reported [251], and the time it takes to gather data reinforces the need to look for simple questionnaires that can serve as easy-to-use PROM in the office and at the bedside. Otherwise, gathering data to build evidence or to have information about each patient will always be very difficult.

For future work it would be important to strengthen the power of these tests to evaluate the patients' well-being, namely through research with a bigger sample and a longitudinal, rather than a cross sectional study, for which multicentric studies may be needed. That would give insight about the evolution of scores and the factors that can

influence it on a dynamic perspective. So far, most of the analysis was made after univariate models and the multivariate approach is the next step.

Another angle for which there may be some interest is disclosing the relationship that these PROM have with the current medical indicators that generally are followed when physicians are treating CKD patients.

Also, the study of the impact of medical interventions on PROM scores would give information on the effectiveness of this strategy of targeting surrogate endpoints rather that the distal ones. All these instruments would have practical utility if they consistently proved to be predictors of outcomes, carrying the influence of the patients' circumstances.

Moreover, little is still known about the issue of patients' preferences. Every patient is different from the next and it is not certain that a treatment goal serves the two equally. From the moment a patient is defined as being sick and what should be measured, there must be a search for personalized outcomes when managing a patient with chronic disease, possibly negotiated with the patients and their families. Personalized Medicine is also arising as a new paradigm. To make that possible, solid clinical outcome measures are needed to assess success and failures. That is why physicians should lead this process [279].

In the origin of this project there was the idea of building a Clinical Balanced Scorecard for better management of Chronic Kidney Disease. The conclusions drawn from this work begin to fill in the tables of the "client's perspective". Some of these endpoints that have proven to be predictors of important outcomes and, at the same time, representatives of the patient's characteristics can now be targets for intervention.

The continuing development and endorsement of valid surrogate endpoints will facilitate medical decision, guide clinical research and establish an agenda for accountability in clinical governance, shortening the time for reaction, as it will not be necessary to wait for the more distal endpoints to assess, reinforce or correct decisions.

References

1. Blagg CR. The Early History of Dialysis for Chronic Renal Failure in the United States: A View From Seattle. Am J Kidney Dis 2007;49(3):482-96. doi: 10.1053/j.ajkd.2007.01.017
2. Chan R, Brooks R, Erlich J, et al. The Effects of Kidney-Disease-Related Loss on Long-Term Dialysis Patients' Depression and Quality of Life: Positive Affect as a Mediator. Clin J Am Soc Nephrol 2009;4:160-67. doi: 10.2215/CJN.01520308
3. Finkelstein FO, Finkelstein SH. Depression in Chronic Dialysis Patients: Assessment and Treatment. Nephrol Dial Transplant 2000;15:1911-13.
4. Hercz G. The Trauma of Dialysis Initiation. J Am Soc Nephrol 2017;28:2835–37. doi: 10.1681/ASN.2017020212
5. Sharief S, Hsu C. The Transition From the Pre-ESRD to ESRD Phase of CKD: Much Remains to Be Learned. Am J Kidney Dis 2017;69(1):8-10. doi: 10.1053/j.ajkd.2016.10.001
6. Saini T, Murtagh FE, Dupont PJ, et al. Comparative Pilot Study of Symptoms and Quality of Life in Cancer Patients and Patients with End Stage Renal Disease. Palliat Med 2006;20(6):631-6. doi: 10.1177/0269216306070236
7. Oreopoulos D, Dimkovic N. Geriatric Nephrology is Coming of Age. J Am Soc Nephrol 2003;14(4):1099-101. doi: 10.1097/01.ASN.0000067656.48829.0E
8. Carson RC, Juszczak M, Davenport A, et al. Is Maximum Conservative Management an Equivalent Treatment Option to Dialysis for Elderly Patients with Significant Comorbid Disease? Clin J Am Soc Nephrol 2009;4(10):1611-9. doi: 10.2215/CJN.0051010
9. Klein O, Korzets Z, Bernheim J. Is a Major Psychiatric Illness a Contraindication to Chronic Dialysis? Nephrol Dial Transplant 2005;20(12):2608-10. doi: 10.1093/ndt/gfi147
10. Cooper BA, Branley P, Bulfone L, et al. A Randomized, Controlled Trial of Early versus Late Initiation of Dialysis. N Engl J Med 2010;363:609-19. doi: 10.1056/NEJMoa1000552
11. Tattersall J, Dekker F, Heimbürger O, et al. When to Start Dialysis: Updated Guidance Following Publication of the Initiating Dialysis Early and Late (IDEAL) Study. Nephrol Dial Transplant 2011;6:2082–86. doi: 10.1093/ndt/gfr168
12. Kaplan RS, Norton D. The Balanced Scorecard – Measures That Drive Performance. Harv Bus Rev 1992;70(1):71-79.
13. Deshpande PR, Rajan S, Sudeepthi BL, et al. Patient Reported Outcomes: A New Era in Clinical Research. Perspect Clin Res 2011;2(4):137-44. doi: 10.4103/2229-3485.86879
14. Aiyegbusi OL, Kyte D, Cockwell P, et al. Using Patient-Reported Outcome Measures (PROMs) to Promote Quality of Care and Safety in the Management of Patients with Advanced Chronic Kidney Disease (PRO-trACK project): a Mixed-methods Project Protocol. BMJ 2017;7(7) doi: 10.1136/bmjopen-2017-016687
15. Kalantar-Zadeh K, Unruh M. Health Related Quality of Life in Patients with Chronic Kidney Disease. Int Urol Nephrol 2005;37(2):367-78. doi: 10.1007/s11255-004-0012-4
16. National Kidney Foundation. K/DOQI Clinical Practice Guidelines for Chronic Kidney Disease: Evaluation, Classification, and Stratification. Am J Kidney Dis 2002;39(2 Suppl 1):S1-266.
17. Levey AS, Coresh J. Chronic Kidney Disease. Lancet 2012;379:165-80. doi: 10.1016/S0140-6736(11)60178-5
18. Bricker NS, Morrin PA, Kime SW. The Pathologic Physiology of Chronic Bright's Disease. An Exposition of the 'Intact Nephron Hypothesis'. Am J Med 1960;28:77-98. doi: 10.1016/0002-9343(60)90225-4
19. Levey AS, de Jong PE, Coresh J, et al. The Definition, Classification and Prognosis of Chronic Kidney Disease: a KDIGO Controversies Conference report. Kidney Int 2011;80(1):17-28. doi: 10.1038/ki.2010.483
20. National Kidney Foundation. NKF-DOQI Guideline Development Methodology. Am J Kidney Dis 1997;30(4):S142-S47. doi: 10.1016/S0272-6386(97)90248-1
21. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney inter., Suppl. 2013; 3: 1–150. Kidney Inter Suppl 2013;3:1-150. doi: 10.1038/kisup.2012.76

22. Levey AS, Stevens LA, Coresh J. Conceptual Model of CKD: Applications and Implications. American Journal of Kidney Disease 2009;53(S4):S4-S16. doi: 10.1053/j.ajkd.2008.07.048
23. Van der Velde M, Matsushite K, Coresh J. Lower Estimated Glomerular Filtration Rate and Higher Albuminuria are Associated with All-Cause and Cardiovascular Mortality. A Collaborative Meta-Analysis of High Risk Population Cohorts. Kidney Int 2011;79(12):1341-52. doi: 10.1038/ki.2010.536
24. Hill NR FS, Oke JL, Hirst JA, O'Callaghan CA, Lasserson DS, et al. Global Prevalence of Chronic Kidney Disease– A Systematic Review and Meta-Analysis. PLoS ONE 2016;11(7):e0158765.
25. United States Renal Data System. Chapter 11: Medicare Expenditures for Persons with ESRD. In: National Institutes of Health NIoDaDaKD, ed. Annual Data Report. Bethesda, MD., 2016.
26. Kerr M, Bray B, Medcalf J, et al. Estimating the Financial Cost of Cchronic Kidney Disease to the NHS in England. Nephrol Dial Transplant 2012;27(Suppl 3):iii73–iii80. doi: 10.1093/ndt/gfs269
27. United States Renal Data System. Annual Data Report: Epidemiology of Kidney Disease in the United States. Bethesda, MD: National Institute of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 2017.
28. White SL, Chadban SJ, Jan S, et al. How Can We Achieve Global Equity in Provision of Renal Replacement Therapy? Bull World Health Organ 2008;86(3):161-240. doi: 10.2471/BLT.07.041715]
29. Coresh J, Byrd-Holt D, Astor BC, et al. Chronic Kidney Disease Awareness, Prevalence, and Trends Among U.S. Adults, 1999 to 2000. J Am Soc Nephrol 2005;16(1):180-8. doi: 10.1681/ASN.2004070539
30. Coresh J, Astor BC, Greene T, et al. Prevalence of Chronic Kidney Disease and Decreased Kidney Function in the Adult US Population: Third National Health and Nutrition Examination Survey. American Journal of Kidney Disease 2003;41(1):1-12. doi: 10.1053/ajkd.2003.50007
31. Liyanage T, Ninomiya T, Jha V. Worldwide Access to Treatment for End-Stage Kidney Disease: a Systematic Review. Lancet 2015;385:1975. doi: 10.1016/S0140-6736(14)61601-9
32. McClellan W, Warnock DG, McClure L, et al. Racial Differences in the Prevalence of Chronic Kidney Disease among Participants in the Reasons for Geographic and Racial Differences in Stroke (REGARDS) Cohort Study. J Am Soc Nephrol 2006;17(6):1710-15. doi: 10.1681/ASN.2005111200
33. Emdin CA, Anderson SG, Woodward M, et al. Usual Blood Pressure and Risk of New-Onset Diabetes: Evidence From 4.1 Million Adults and a Meta-Analysis of Prospective Studies. J Am Coll Cardiol 2015;66(14):1552-56. doi: 10.1016/j.jacc.2015.07.059
34. James PA, Oparil S, Carter BL, et al. Evidence-Based Guideline for the Management of High Blood Pressure in Adults - Report From the Panel Members Appointed to the Eighth Joint National Committee (JNC 8). JAMA 2014;311(5):507-20. doi: 10.1001/jama.2013.284427
35. Klag M. Blood Pressure and End-Stage Renal Disease. N Engl J Med 1996;334(1):13-18. doi: 10.1056/NEJM199601043340103
36. Gabinete de Registo da Doença Renal Terminal. Portuguese Registry of Dialysis and Transplantation 2017. In: Macário F, Filipe R, Lopes JA, et al., eds.: Sociedade Portuguesa de Nefrologia, 2018.
37. Azar M. The Elderly Patient with Low eGFR: Beyond the Numbers. Rhode Island Medical Journal 2014;97(12):19-23.
38. Winearls C, Haynes R, Glassock R. CKD Staging-Evolution Not Revolution. Nefrologia 2010;30(5):493-500. doi: 10.3265/Nefrologia.pre2010.Jul.10501
39. Evans PD, Taal MW. Epidemiology and Causes of Chronic Kidney Disease. Medicine 2015;3943(8):450-52. doi: 10.1016/j.mpmed.2015.05.005
40. Jha V, Garcia-Garcia G, Iseki K, et al. Chronic Kidney Disease: Global Dimension and Perspectives. The Lancet 2013;382(9888):260-72. doi: 10.1016/S0140-6736(13)60687-X
41. Naughton C. Drug-Induced Nephrotoxicity. Am Fam Physician 2008;78(6):743-50.
42. Vehaskari VM. Genetics and CKD. Adv Chronic Kidney Dis 2011;18(5):317-23. doi: 10.1053/j.ackd.2011.07.001
43. Naik RP, Derebail V, Grams M, et al. Association of Sickle Cell Trait With Chronic Kidney Disease and Albuminuria in African Americans. JAMA 2014;312(20):2115-25. doi: 10.1001/jama.2014.15063
44. Rambausek M, Hartz G, Waldherr R, et al. Familial Glomerulonephritis. Pediatr Nephrol 1987;1(1):416-8.
45. Ronco C, McCullough P, Anker SD, et al. Cardio-Renal Syndromes: Report from the Consensus Conference of the Acute Dialysis Quality Initiative. Eur Heart J 2010;31:703-11. doi: 10.1093/eurheartj/ehp507
46. García-Donaire JA, Ruilope LM. Cardiovascular and Renal Links along the Cardiorenal Continuum. Int J Nephrol 2011:975782. doi: 10.4061/2011/975782

47. Shah BN, Greaves K. The Cardiorenal Syndrome: A Review. Int J Nephrol Renovasc Dis 2011 doi: 10.4061/2011/920195
48. Ronco C, Haapio M, House AA, et al. Cardiorenal Syndrome. J Am Coll Cardiol 2008;52(19):1527-39. doi: 10.1016/j.jacc.2008.07.051
49. Hadjiphilippou S, Kon SP. Cardiorenal Syndrome: Review of Our Current Understanding. J R Soc Med 2015;109(1):12-17. doi: 10.1177/0141076815616091
50. Di Lullo L, Bellasi A, Barbera V, et al. Pathophysiology of the Cardio-Renal Syndromes Types 1-5: An Uptodate. Indian Heart J 2017;69(2):255-65. doi: 10.1016/j.ihj.2017.01.005
51. Tsimihodimos V, Mitrogianni Z, Elisaf M. Dyslipidemia Associated with Chronic Kidney Disease. Open Cardiovasc Med J 2011; 5:41-48. doi: 10.2174/1874192401105010041
52. Stenvinkel P, Zoccali C, Ikizler TA. Obesity in CKD—What Should Nephrologists Know? JASN 2013;24(11):1727-36. doi: 10.1681/ASN.2013040330
53. Staplin N. Smoking and Adverse Outcomes in Patients With CKD: The Study of Heart and Renal Protection (SHARP). Am J Kidney Dis 2016;68(3):371-80. doi: 10.1053/j.ajkd.2016.02.052
54. Orth SR, Schroeder T, Ritz E, et al. Effects of Smoking on Renal Function in Patients With Type 1 and Type 2 Diabetes Mellitus. Nephrol Dial Transplant 2005;20(11):2414-19. doi: 10.1093/ndt/gfi022
55. Foster MC, Hwang SJ, Larson MG. Overweight, Obesity and the Development of Stage 3 CKD: the Framimghm Heart Study. American Journal of Kidney Disease 2008;52(1):39–48. doi: 10.1053/j.ajkd.2008.03.003
56. Lunyera J, Mohottige D, Von Isenburg M, et al. CKD of Uncertain Etiology: A Systematic Review. Clin J Am Soc Nephrol 2016;11:379-85. doi: 10.2215/CJN.07500715
57. Varughese S, Abraham G. Chronic Kidney Disease in India. A Clarion Call for Change. Clin J Am Soc Nephrol 2018;13: CJN.09180817. doi: 10.2215/CJN.09180817
58. Fogo A. Mechanisms of Progression of Chronic Kidney Disease. Pediatr Nephrol 2007;22(12):2011-22. doi: 10.1007/s00467-007-0524-0
59. Hostetter TH, Olson JL, Rennke HG, et al. Hyperfiltration in Remnant Nephrons: A Potentially Adverse Response to Renal Ablation. Am J Physiol 1981;241:F85-F93. doi: 10.1152/ajprenal.1981.241.1.F85
60. Manrique C, Lastra G, Gardner M, et al. The Renin Angiotensin Aldosterone System in Hypertension: Roles of Insulin Resistance and Oxidative Stress. Med Clin North Am 2009;93(3):569-82. doi: 10.1016/j.mcna.2009.02.014
61. Fabre J, Balant L. Renal Failure, Drug Pharmacokinetics and Drug Action. Clin Pharmacokinetics 1976;1(2):99-120.
62. Lisowska-Myjak B. Uremic Toxins and Their Effects on Multiple Organ Systems. Nephron Clin Pract 2014;128:303-11. doi: 10.1159/000369817
63. EUTox Work Group. Uremic Toxin Database [accessed 30 Nov 2016].
64. Stinghen AEM, Pecoits-Filho R. Vascular Damage in Kidney Disease: Beyond Hypertension. Int J Hypertens 2011 doi: 10.4061/2011/232683
65. Lemley KV, Kriz W. Anatomy of the Renal Interstitium. Kidney Int 1991;39(3):370-81.
66. Fogo A, Lusco MA, Najafian B, et al. AJKD Atlas of Renal Pathology: Chronic Interstitial Nephritis. Am J Kidney Dis 2017;70(e1-e2) doi: 10.1053/j.ajkd.2017.05.002
67. Sandilands EA, Dhaun N, Dear JW, et al. Measurement of Renal Function in Patients with Chronic Kidney Disease. Br J Clin Pharmacol 2013;76(4):505-15. doi: 10.1111/bcp.12198
68. Schaeffner E. Determining the Glomerular Filtration Rate—An Overview. J Ren Nutr 2017;27(6):375-80. doi: 10.1053/j.jrn.2017.07.005
69. Annet L, Hermoye L, Peeters F, et al. Glomerular Filtration Rate: Assessment With Dynamic Contrast-Enhanced MRI and a Cortical Compartment Model in the Rabbit Kidney. J Magn Reson Imaging 2004;20:843-49. doi: 10.1002/jmri.20173
70. Stevens LA, Coresh J, Greene T, et al. Assessing Kidney Function — Measured and Estimated Glomerular Filtration Rate. N Engl J Med 2006;354:2473-83. doi: 10.1056/NEJMra054415
71. Seldin DW. The Development of the Clearance Concept. Journal of Nephrology 2004;17(1):166-71.
72. Jones G, Lim EM. The National Kidney Foundation Guideline on Estimation of the Glomerular Filtration Rate. Clin Biochem Rev 2003;24(3):95-98.
73. Cockcroft DW, Gault MH. Prediction of Creatinine Clearance from Serum Creatinine. Nephron 1976;16(1):31-41. doi: 10.1159/000180580

74. Levey AS, Bosch JP, Lewis JB, et al. A More Accurate Method to Estimate Glomerular Filtration Rate From Serum Creatinine: A New Prediction Equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med 1999;130(6):461-70. doi: 10.7326/0003-4819-130-6-199903160-00002
75. Levey AS, Coresh J, Greene T, et al. Using Standardized Serum Creatinine Values in the Modification of Diet in Renal Disease Study Equation for Estimating Glomerular Filtration Rate. Ann Intern Med 2006;145(4):247-54. doi: 10.7326/0003-4819-145-4-200608150-00004
76. Levey AS, Stevens LA, Schmid CH, et al. CKD-EPI (Chronic Kidney Disease Epidemiologic Collaboration). A New Equation to Estimate Glomerular Filtration Rate. Ann Intern Med 2009;150(9):604-12. doi: 10.7326/0003-4819-150-9-200905050-00006
77. Cristelli MP, Cofán F, Rico N, et al. Estimation of Renal Function by CKD-EPI versus MDRD in a Cohort of HIV-Infected Patients: a Cross-Sectional Analysis. BMC Nephrol 2017;18:58. doi: 10.1186/s12882-017-0470-4
78. Mangione F, Dal Canton AD. Chronic Kidney Disease Epidemic: Myth and Reality. Intern Emerg Med 2011;6(Suppl 1):S69-S76. doi: 10.1007/s11739-011-0686-4
79. Vervoort G, Willems HL, Wetzels JF. Assessment of glomerular filtration rate in healthy subjects and normoalbuminuric diabetic patients: validity of a new (MDRD) prediction equation. Nephrol Dial Transplant 2002;17(11):1909-13.
80. Coresh J, Stevens LA. Kidney Function Estimating Equations: Where Do We Stand? Curr Opin Nephrol Hypertens 2006;15(3):276-84. doi: 10.1097/01.mnh.0000222695.84464.61
81. Schwartz GJ, Haycock GB, Edelmann C, Jr, et al. A Simple Estimate of Glomerular Filtration Rate in Children Derived From Body Length and Plasma Creatinine. Pediatrics 1976;58(2):259-63.
82. Schwartz GJ, Muñoz A, Schneider MF, et al. New Equations to Estimate GFR in Children with CKD. J Am Soc Nephrol 2009;20(3):629-37. doi: 10.1681/ASN.2008030287
83. Pottel H, Hoste L, Dubourg L, et al. An Estimated Glomerular Filtration Rate Equation For the Full Age Spectrum. Nephrol Dial Transplant 2016;31(5):798.806. doi: 10.1093/ndt/gfv454
84. Björk J, Jones I, Nyman U, et al. Validation of the Lund–Malmö, Chronic Kidney Disease Epidemiology (CKD-EPI) and Modification of Diet in Renal Disease (MDRD) Equations to Estimate Glomerular Filtration Rate in a Large Swedish Clinical Population. Scand J Urol Nephrol 2012;46(3):212-22. doi: 10.3109/00365599.2011.644859
85. Nyman U, Grubb A, Larsson A, et al. The Revised Lund-Malmö GFR Estimating Equation Outperforms MDRD and CKD-EPI Across GFR, Age and BMI Intervals in a Large Swedish Population. Clin Chem Lab Med 2014;52(6):815-24. doi: 10.1515/cclm-2013-0741
86. Robles NR, Felix FJ, Fernandez-Berges D, et al. The HUGE Formula (Hematocrit, Urea and Gender): Association with Cardiovascular Risk. Eur Rev Med Pharmacol Sci 2013;17(14):1889-93.
87. Alvarez-Gregori JA, Robles NR, Mena C, et al. The Value of a Formula Including Haematocrit, Blood Urea and Gender (HUGE) as a Screening Test for Chronic Renal Insufficiency. The Journal of Nutrition, Health and Aging 2011;15(6):480-84.
88. Rule AD, Larson TS, Bergstralh EJ, et al. Using Serum Creatinine To Estimate Glomerular Filtration Rate: Accuracy in Good Health and in Chronic Kidney Disease. Ann Intern Med 2004;141:929-37. doi: 10.7326/0003-4819-141-12-200412210-00009
89. Shemesh O, Golbetz H, Kriss JP, et al. Limitations of Creatinine as a Filtration Marker in Glomerulopathic Patients. Kidney Int 1985;28(5):830-38.
90. Rosansky SJ. Renal Function Trajectory is More Important than Chronic Kidney Disease Stage for Managing Patients with Chronic Kidney Disease. Am J Nephrol 2012;36(1):1-10. doi: 10.1159/000339327
91. Bassareo PP, Fanos V, Mussap M, et al. Urinary NGAL and Hematic ADMA Levels: An Early Sign of Cardio-Renal Syndrome in Young Adults Born Preterm? J Matern Fetal Neonatal Med 2013;26 Suppl 2:80-83. doi: 0.3109/14767058.2013.829698
92. Inker L, AS; L. Staging and Management of Chronic Kidney Disease. In: Gilbert SJ, Weiner DE, Gipson DS, et al., eds. Primer on Kidney Diseases. 6th ed. Philadelphia: Elsevier Saunders 2014.
93. Coresh J. CKD Prognosis: Beyond the Traditional Outcomes. Am J Kidney Dis 2009;54(1):1-3. doi: 10.1053/j.ajkd.2009.05.005

94. Bello AK, Alrukhaimi M, Ashuntantang GE, et al. Complications of Chronic Kidney Disease: Current State, Knowledge Gaps, and Strategy for Action. Kidney International Supplements 2017;7(2):122-29. doi: 10.1016/j.kisu.2017.07.007
95. Sakhuja A, Hyland J, JF. S. Managing Advanced Chronic Kidney Disease: a Primary Care Guide. Cleve Clin J Med 2014;81(5):289-99. doi: 10.3949/ccjm.81a.13046
96. European Best Practice Guidelines. Guideline I.2 When to Refer to a Nephrology Clinic Nephrol Dial Transplant 2002;17(suppl 7):9-10. doi: 10.1093/ndt/17.suppl_7.9
97. Chan MR, Dall AT, KE F. Outcomes in Patients with CKD Referred Late to Nephrologists: a Meta Analysis. Am J Med 2007;120 doi: 10.1016/j.amjmed.2007.04.024
98. de Jager DJ, Voormolen N, Krediet RT, et al. Association Between Time of Referral and Survival in the First Year of Dialysis in Diabetics and the Elderly. Nephrology, Dialysis and Transplantation 2011;26(2):652-58. doi: 10.1093/ndt/gfq438
99. Rastogi A, Linden A, Nissenson A. Disease Management in Chronic Kidney Disease. Adv Chronic Kidney Dis 2008;15(1):19-28. doi: 10.1053/j.ackd.2007.10.011
100. Ward BW, Schiller JS, Goodman RA. Multiple Chronic Conditions Among US Adults: A 2012 Update. Prev Chronic Dis 2014;11:1390389. doi: 10.5888/pcd11.130389
101. CDC, Center for Diseases Control and Prevention. National Center for Health Statistics. Health, United States, 2015: With Special Feature on Racial and Ethnic Health Disparities. Hyattsville, MD., 2016.
102. European Observatory on Health Systems and Policies. Caring for people with chronic conditions - A health system perspective: Open University Press 2008.
103. Bernell S, Howard SW. Use Your Words Carefully: What Is a Chronic Disease? Front Public Health 2016;4:159. doi: 10.3389/fpubh.2016.00159
104. Covinsky KE, Eng C, Lui LY, et al. The Last 2 Years of Life: Functional Trajectories of Frail Older People. J Am Geriatr Soc 2003;51(4):492-98. doi: 10.1046/j.1532-5415.2003.51157.x
105. Glasgow RE, Orleans CT, Wagner EH. Does the Chronic Care Model Serve Also as a Template for Improving Prevention? The Milbank Quarterly 2001;79(4):579-612. doi: 10.1111/1468-0009.00222
106. CDC, Centers for Disease Control and Prevention. National Center for Chronic Disease Prevention and Health Promotion [Available from: www.cdc.gov/chronicdisease/index.htm# accessed 26 Mar 2017].
107. Maaravi Y, Cohen A, Hammerman-Rozenberg R, et al. Home Hospitalization. J Am Med Dir Assoc 2002;3(2):114-8. doi: 10.1016/S1525-8610(04)70424-7
108. Leff B, Burton L, Guido S, et al. Home Hospital Program: a Pilot Study. J Am Geriatr Soc 1999;47(6):697-702. doi: 10.1111/j.1532-5415.1999.tb01592.x
109. Rome RB, Luminais HH, Bourgeois DA, et al. The Role of Palliative Care at the End of Life. Ochsner J 2011;11(4):348-52.
110. Grover A, Joshi A. An Overview of Chronic Disease Models: A Systematic Literature Review Global Journal of Health Science 2015;7(2) doi: 10.5539/gjhs.v7n2p210
111. Bauer U, Briss PA, Goodman RA, et al. Prevention of Chronic Disease in the 21st Century: Elimination of the Leading Preventable Causes of Premature Death and Disability in the USA. Lancet 2014;384:45-52. doi: 10.1016/S0140-6736(14)60648-6
112. Working Group on Health Outcomes for Older Persons With Multiple Chronic Conditions. Universal Health Outcome Measures for Older Persons with Multiple Chronic Conditions. J Am Geriatr Soc 2012;60(12):2333-41. doi: 10.1111/j.1532-5415.2012.04240.x
113. Porter ME. What Is Value in Health Care? N Engl J Med 2010;363:2477-81 doi: 10.1056/NEJMp1011024
114. Donabedian A. Evaluating the Quality of Medical Care. The Milbank Quarterly 2005;83(4):691-729. doi: 10.1111/j.1468-0009.2005.00397.x
115. Smith R. Medicine's Need for Kaizen. BMJ 1990;301:679-80. doi: 10.1136/bmj.301.6754.679
116. Imai M. Gemba Kaizen: A Commonsense Approach to a Continuous Improvement Strategy, Second Edition: McGraw-Hill 2012.
117. WHO. Constitution of the World Health Organization 1948 [Available from: www.who.int/governance/eb/who_constitution_en.pdf].
118. Eberst RM. Defining Health: A Multidimensional Model. J Sch Health 1984;54(3):99-104. doi: 10.1111/j.1746-1561.1984.tb08780.x

119. Pais-Ribeiro JL. Quality of Life is a Primary End-point in Clinical Settings. Clin Nutr 2004;23:121-30. doi: 10.1016/S0261-5614(03)00109-2
120. WHOQOL Group. Development of the WHOQOL: Rationale and Current Status. Int J Ment Health 1994;23(3):24-56. doi: 10.1080/00207411.1994.11449286
121. Revicki DA, Osoba D, Fairclough D, et al. Recommendations on Health-Related Quality of Life Research to Support Labeling and Promotional Claims in the United States. Qual Life Res 2000;9:887-900. doi: 10.1023/A:1008996223999
122. Gill TM, Feinstein AR. A Critical Appraisal of the Quality-of-Life Measurements. JAMA 1994;272(8):619-26. doi: 10.1001/jama.1994.03520080061045
123. Adunuri NR, Feldman BM. Critical Appraisal of Studies Measuring Quality of Life in Juvenile Idiopathic Arthritis. Arthritis Care Res (Hoboken) 2015;67(6):880-84. doi: 10.1002/acr.22514
124. Weinstein MC, Torrance G, McGuire A. QALYs: The Basics. Value Health 2009;12(Suppl 1):S5-S9. doi: 10.1111/j.1524-4733.2009.00515.x
125. Gold MR, Stevenson D, Fryback DG. HALYs and QALYs and DALYs, Oh My: Similarities and Differences in Summary Measures of Population Health. Annu Rev Public Health 2002;23:115-34. doi: 10.1146/annurev.publhealth.23.100901.140513
126. Burström K, Johannesson M, Diderichsen F. A Comparison of Individual and Social Time Trade-off Values for Health States in the General Population. Health Policy 2006;76(3):359-70. doi: 10.1016/j.healthpol.2005.06.011
127. Dolan P, Gudex C, Kind P, et al. The Time Trade-off Method: Results from a General Population Study. Health Econ 1996;5:141-54. doi: 10.1002/(SICI)1099-1050(199603)5:2<141::AID-HEC189>3.0.CO;2-N
128. Whitehead SJ, Ali S. Health Outcomes in Economic Evaluation: the QALY and Utilities. Br Med Bull 2010;96(1):5-21. doi: 10.1093/bmb/ldq033
129. Ogden J. QALY and Their Role in the NICE Decision-Making Process. Prescriber uk 2017;41-43.
130. Goldberg R, Gore JM, Barton B, et al. Individual and Composite Study Endpoints: Separating the Wheat from the Chaff. Am J Med 2014;127(5):379-84. doi: 10.1016/j.amjmed.2014.01.011
131. Valderas JM, Starfield B, Sibbald B, et al. Defining Comorbidity: Implications for Understanding Health and Health Services. Ann Fam Med 2009;7(4):357-63. doi: 10.1370/afm.983
132. Charlson ME, Pompei P, Ales KL, et al. A New Method of Classifying Prognostic Comorbidity in Longitudinal Studies: Development and Validation. J Chronic Dis 1987;40(5):373-83.
133. Quan H, Li B, Couris C, et al. Updating and Validating the Charlson Comorbidity Index and Score for Risk Adjustment in Hospital Discharge Abstracts Using data From 6 Countries. Am J Epidemiol 2011;173:676-82. doi: 10.1093/aje/kwq433
134. Davies SJ, Phillips L, Naish PF, et al. Quantifying Comorbidity in Peritoneal Dialysis Patients and its Relationship to Other Predictors of Survival. Nephrol Dial Transplant 2002;17(6):1.
135. Fried L, Bernardini J, Piraino B. Comparison of the Charlson Comorbidity Index and the Davies Score as a Predictor of Outcomes in PD Patients. Perit Dial Int 2003;23:568-73.
136. Greene T, Beck GJ, Gassman JJ, et al. Design and Statistical Issues of the Hemodialysis (HEMO) Study. Control Clin Trials 2000;21:502-25.
137. Miskulin DC, Athienites NV, Yan G, et al. Comorbidity Assessment Using the Index of Coexistent Diseases in a Multicenter Clinical Trial. Kidney Int 2001;60(4):1498-510. doi: 10.1046/j.1523-1755.2001.00954.x
138. Greenfield S, Apolone G, McNeil BJ, et al. The Importance of Co-Existent Disease in the Occurrence of Postoperative Complications and One-year Recovery in Patients Undergoing Total Hip Replacement. Comorbidity and Outcomes After Hip Replacement. Med Care 1993;31(2):141-54.
139. Bayliss EA, Ellis JL, Steiner JF. Subjective Assessments of Comorbidity Correlate with Quality of Life Health Outcomes: Initial validation of a Comorbidity Assessment Instrument. Health and Quality of Life Outcomes 2005;3:51. doi: 10.1186/1477-7525-3-51
140. Gilson B, Gilson J, Bergner M, et al. The Sickness Impact Profile. Development of an Outcome Measure of Health Care. American Journal of Kidney Disease 1975;65(12):1304-10.
141. de Bruin AF, Buys M, de Witte LP, et al. The Sickness Impact Profile: SIP68, a Short Generic Version. First evaluation of the Reliability and Reproducibility. J Clin Epidemiol 1994;47(8):863-71. doi: 10.1016/0895-4356(94)90189-9

142. Nanda U, McLendon PM, Andresen EM, et al. The SIP68: an Abbreviated Sickness Impact Profile for Disability Outcomes Research. Qual Life Res 2003;12(5):583-95. doi: 10.1023/A:1025036325886
143. Food and Drug Administration. Guidance for Industry. Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims: FDA, 2009.
144. Chen J. Integrated Care. Patient Reported Outcome Measures and Patient Reported Experience Measures, a Rapid Scoping Review: Agency of Clinical Innovation, New South Wales, Australia, 2017.
145. National Quality Forum. Measure Evaluation Criteria 2012 [Available from: www.qualityforum.org/measuring_performance/submitting_standards/measure_evaluation_criteria.aspx accessed 01Oct2018].
146. Cella D, Yount S, Rothrock N, et al. The Patient-Reported Outcomes Measurement Information System (PROMIS). Med Care 2007;45(5 suppl 1):S3-S11. doi: 10.1097/01.mlr.0000258615.42478.55
147. Witter J. Introduction: PROMIS a First Look Across Diseases. J Clin Epidemiol 2016;73:87-88. doi: 10.1016/j.jclinepi.2016.02.014
148. Ader DN. Developing the Patient-Reported Outcomes Measurement Information System (PROMIS). Med Care 2007;45(4) doi: 10.1097/01.mlr.0000260537.45076.74
149. Northwestern University. HealthMeasures: Intro to PROMIS®. 2017 [Available from: www.healthmeasures.net/explore-measurement-systems/promis/intro-to-promis) accessed 09JUL2018].
150. McHorney CA, Ware J, Jr, , Raczek AE. The MOS 36-Item Short-Form Health Survey (SF-36): II. Psychometric and Clinical Tests of Validity in Measuring Physical and Mental Health Constructs. Med Care 1993;31:247-63.
151. Pyne JM, Sieber WJ, David K, et al. Use of the Quality of Well-Being Self-Administered Version (QWB-SA) in Assessing Health-Related Quality of Life in Depressed Patients. J Affect Disord 2003;76:237-47. doi: 10.1016/S0165-0327(03)00106-X
152. The WHOQOL Group. Development of the World Health Organization WHOQOL-BREF Quality of Life Assessment. Psychol Med 1998;28(3):551-58.
153. Devins GM. Using the Illness Intrusiveness Ratings Scale to Understand Health-Related Quality of Life in Chronic Disease. J Psychosom Res 2010;68(6):591-602. doi: 10.1016/j.jpsychores.2009.05.006
154. Kroenke K, Spitzer R, Williams J. The PHQ-9: Validity of a Brief Depression Severity Measure. J Gen Intern Med 2001;16(9):606-13. doi: 10.1046/j.1525-1497.2001.016009606.x
155. Wright EP, Kiely M, Johnson C, et al. Development and Evaluation of an Instrument to Assess Social Difficulties in Routine Oncology Practice. Qual Life Res 2005;14(373-386) doi: 10.1007/s11136-004-5332-4
156. Spitzer R, Kroenke K, Williams JB, et al. A Brief Measure for Assessing Generalized Anxiety Disorder: the GAD-7. Arch Intern Med 2006;166(10):1092-97. doi: 10.1001/archinte.166.10.1092
157. Bruera E, Kuehn N, Miller MJ, et al. The Edmonton Symptom Assessment System (ESAS): a Simple Method for the Assessment of Palliative Care Patients. J Palliat Care 1991;7(2):6-9.
158. Johns MW. A New Method for Measuring Daytime Sleepiness: the Epworth Sleepiness Scale. Sleep 1991;14:50-55.
159. Allen RP, Burchell BJ, MacDonald B, et al. Validation of the Self-Completed Cambridge-Hopkins Questionnaire (CH-RLSq) for Ascertainment of Restless Legs Syndrome (RLS) in a Population Survey. Sleep 2009;10(10):1097-100. doi: 10.1016/j.sleep.2008.10.007
160. Gorodetskaya I, Zenios S, Mcculloch CE, et al. Health-Related Quality of Life and Estimates of Utility in Chronic Kidney Disease. Kidney Int 2005;68(6):2801-08. doi: 10.1111/j.1523-1755.2005.00752.x
161. Johnson JA, Coons SJ, Ergo A, et al. Valuation of EuroQOL (EQ-5D) Health States in an Adult US Sample. Pharmacoeconomics 1998;13(4):421-33. doi: 10.2165/00019053-199813040-00005
162. EuroQol Group. EuroQol-a New Facility for the Measurement of Health-Related Quality of Life. Health Policy 1990;16(3):199-208. doi: 10.1016/0168-8510(90)90421-9
163. Ciampi A, Lockwood G, Sutherland HJ, et al. Assessment of Health-Related Quality of Life. Factor Scales for Patients with Breast Cancer. J Psychosoc Oncol 1989;6(1):2.
164. Ferrans CE, Powers MJ. Quality of Life Index: Development and Psychometric Propeties. Advances in Nursing Science 1985;8(1):15-24.
165. Hays RD, Kallich JD, Mapes DL, et al. Development of the Kidney Disease Quality of Life Instrument. Qual Life Res 1994;3(5):329-38. doi: 10.1007/BF00451725

166. Laupacis A, Muirhead N, Keown P, et al. A Disease-Specific Questionnaire for Assessing Quality of Life in Patients on Hemodialysis. Nephron 1992;60:302-06. doi: 10.1159/000186769
167. Laupacis A, Pus N, Muirhead N, et al. Disease-specific Questionnaire for Patients with a Renal Transplant. Nephron 1993;64(2):226-31. doi: 10.1159/000187318
168. Aawar N, Moore R, Riley S, et al. Interpretation of Renal Quality of Life Profile Scores in Routine Clinical Practice: an Aid to Treatment Decision-Making. Qual Life Res 2016;25:1697-702. doi: 10.1007/s11136-015-1191-4
169. Wu AW, Fink NE, Cagney KA, et al. Developing a Health-Related Quality-of-Life Measure for End-Stage Renal Disease: The CHOICE Health Experience Questionnaire. Am J Kidney Dis 2001;137(1):11-21. doi: 10.1053/ajkd.2001.20631
170. Bradley C. Design of a Renal-Dependent Individualized Quality of Life Questionnaire. Adv Perit Dial 1997;13:116-20.
171. Maslow AH. A Theory of Human Motivation. Psychol Rev 1943;50(4):370-96. doi: 10.1037/h0054346
172. Guralnik JM, Simonsick EM, Ferrucci L, et al. A Short Physical Performance Battery Assessing Lower Extremity Function: Association with Self-Reported Disability and Prediction of Mortality and Nursing Home Admission. J Gerontol 1994;49(2):M85-94. doi: 10.1093/geronj/49.2.M85
173. Salzberg M. First-in-Human Phase 1 Studies in Oncology: The New Challenge for Investigative Sites. Rambam Maimonides Med J 2012;3(2) doi: 10.5041/RMMJ.1074
174. van Dulmen SA, van der Wees PJ, Bart-Staal JB, et al. Patient Reported Outcome Measures (PROMs) for Goalsetting and Outcome Measurement in Primary Care Physiotherapy, an Explorative Field Study. Physiotherapy 2017;103(1) doi: 10.1016/j.physio.2016.01.001
175. Weenink JW, Braspenning J, Wensing M. Patient Reported Outcome Measures (PROMs) in Primary Care: an Observational Pilot Study of Seven Generic Instruments. BMC Fam Pract 2014;15:88. doi: doi: 10.1186/1471-2296-15-88.
176. Gibbons E, Fitzpatrick R. A Stuctured Review of Patient-Reported Outcome Measures for People with Chronic Kidney Disease - Patient-Reported Outcome Measurement Group: University of Oxford, 2010.
177. NHS England. National PROMs Programme Guidance. In: Insight & Feedback Team NHS England, ed. National PROMs Supplier Accreditation Process. Leeds, 2017.
178. Karnofsky DA, Burchenal JH. The Clinical Evaluation of Chemotherapeutic Agents in Cancer. In: MacLeod CM, ed. Evaluation of Chemotherapeutic Agents. New York: Columbia University Press 1949:191-205.
179. Oken MM, Creech RH, Tormey DC, et al. Toxicity and Response Criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5(6):649-55.
180. Taylor AE, Olver IN, Sivanthan T, et al. Observer Error in Grading Performance Status in Cancer Patients. Support Care Cancer 1999;7(5):332-5.
181. Abernethy AP, Shelby-James T, Fazekas BS, et al. The Australia-Modified Karnofsky Performance Status (AKPS) Scale: a Revised Scale for Contemporary Palliative Care Clinical Practice. BMC Palliat Care 2005;4:7. doi: 10.1186/1472-684X-4-7
182. Péus D, Newcomb N, Hofer S. Appraisal of the Karnofsky Performance Status and Proposal of a Simple Algorithmic System for its Evaluation. BMC Med Inform Decis Mak 2013;13:72. doi: 10.1186/1472-6947-13-72
183. Murtagh FE, Addington-Hall JM, Higginson IJ. End-Stage Renal Disease: a New Trajectory of Funcional Decline in the Last Year of Life. Journal of the American Geriatric Society 2011;59(2):304-8.
184. Murray SA, Kendall M, Boyd K, et al. Illness Trajectories and Palliative Care. BMJ 2005;330(7498):1007-11. doi: 10.1136/bmj.330.7498.1007
185. Tarlov AR, Ware J, Jr, , Greenfield S, et al. The Medical Outcomes Study. An Application of Methods for Monitoring the Results of Medical Care. JAMA 1989;262(7):925-30. doi: 10.1001/jama.1989.03430070073033
186. Ware JE, Sherbourne CD. The MOS 36-Item Short-Form Health Survey (SF-36). I. Conceptual Framework and Item Selection. Med Care 1992;30(6):473-83.
187. Ferreira PL. Criação da versão portuguesa do MOS SF36. Parte I - Adaptação Cultural e Linguística. Acta Med Port 2000;13:55-66. doi: 10.20344/amp.1760

188. Ferreira PL. Criação da versão portuguesa do MOS SF36. Parte II - Testes de Validação. Acta Med Port 2000;13:119-27. doi: 10.20344/amp.1770
189. Wight JP, Edwards L, Brazier J, et al. The SF36 as an Outcome Measure for Services for End-Stage Renal Failure. BMJ Quality & Safety 1998;7(4):209-21. doi: 10.1136/qshc.7.4.209
190. Lacson E, Xu J, Lin SF, et al. A Comparison of SF-36 and SF-12 Composite Scores and Subsequent Hospitalization and Mortality Risks in Long-Term Dialysis Patients. . Clin J Am Soc Nephrol 2010;5(2):252-60. doi: 10.2215/CJN.07231009
191. Hall RK, Luciano A, Pieper C, et al. Association of Kidney Disease Quality of Life (KDQOL-36) with Mortality and Hospitalization in Older Adults Receiving Hemodialysis. BMC Nephrol 2018;19(11) doi: 10.1186/s12882-017-0801-5.
192. Chiu Y-W, Teitelbaum I, Misra M, et al. Pill Burden, Adherence, Hyperphosphatemia, and Quality of Life in Maintenance Dialysis Patients. Clin J Am Soc Nephrol 2009;4(6):1089-96. doi: 10.2215/CJN.00290109
193. Yang F, Luo N, Lau T, et al. Health-Related Quality of Life in Patients Treated with Continuous Ambulatory Peritoneal Dialysis and Automated Peritoneal Dialysis in Singapore. PharmacoEconomics Open 2017 doi: 10.1007/s41669-017-0046-z
194. Leaf DE, Goldfarb DS. Interpretation and Review of Health-Related Quality of Life Data in CKD Patients Receiving Treatment for Anemia. Kidney Int 2009;75(1):15-24. doi: 10.1038/ki.2008.414
195. Soni RK, Weisbord SD, Unruh ML. Health-Related Quality of Life Outcomes in Chronic Kidney Disease. Curr Opin Nephrol Hypertens 2010;19(2):153-59. doi: 10.1097/MNH.0b013e328335f939.
196. Mujais SK, Story K, Brouillette J, et al. Health-related Quality of Life in CKD Patients: Correlates and Evolution over Time. Clin J Am Soc Nephrol 2009; 4:1293-301. doi: 10.2215/CJN.05541008
197. Campbell KL, Ash S, Bauer JD. The Impact of Nutrition Intervention on Quality of Life in Pre-Dialysis Chronic Kidney Disease Patients. Clin Nutr 2008;27:537-44. doi: 10.1016/j.clnu.2008.05.002
198. Ferreira PL, Ferreira LN, Pereira LN. Contributos para a Validação da Versão Portuguesa do EQ-5D. Acta Med Port 2013;26(6):664-75. doi: 10.20344/amp.1317
199. De Kleijn M. The long way from the International Classification of Impairments, Disabilities and Handicaps (ICIDH) to the International Classification of Functioning, Disability and Health (ICF). Disabil Rehabil 2003;25(11-12):561-64. doi: 10.1080/09638280110110879
200. Üstün TB, Chatterji S, Kostanjsek N, et al. Developing the World Health Organization Disability Assessment Schedule 2.0. Bull World Health Organ 2010;88:815-23. doi: 10.2471/BLT.09.067231
201. WHO. Measuring Health and Disability: Manual for WHO Disability Assessment Schedule (WHODAS 2.0): World Health Organization 2010.
202. Moreira A, Alvarelhão J, Silva AG, et al. Tradução e Validação para Português do WHODAS 2.0 - 12 itens em Pessoas com 55 ou Mais Anos. Revista Portuguesa de Saúde Pública 2015;33(2):179-82. doi: 10.1016/j.rpsp.2015.06.003
203. WHO. WHODAS 2.0 Summary Scores 2018 [Available from: www.who.int/classifications/icf/whodasii/en/index4.html accessed 30th April 2018].
204. Galli T, Mirata P, Foglia E, et al. A Comparison Between WHODAS 2.0 and Modified Barthel Index: Which Tool is More Suitable for Assessing the Disability and the Recovery Rate in Orthopedic Rehabilitation? Clinicoecon Outcomes Res 2018;10:301-07. doi: 10.2147/CEOR.S150526.
205. Yoo JI, Park JS, Kim RB, et al. WHO Disability Assessment Schedule 2.0 is Related to Upper and Lower Extremity Disease-specific Quality of Life. Qual Life Res 2018;27:2243. doi: 10.1007/s11136-018-1869-5
206. Podsiadlo D, Richardson S. The Timed "Up & Go": A Test of Basic Functional Mobility for Frail Elderly Persons. Journal American Geriatrics Society 1991;39(2):142-48. doi: 10.1111/j.1532-5415.1991.tb01616.x
207. Pavasini R, Guralnik J, Brown JC. Short Physical Performance Battery and All-Cause Mortality: Systematic Review and Meta-Analysis. BMC Med 2016;14:215. doi: 10.1186/s12916-016-0763-7
208. den Berg M, Sherrington C, Killington M, et al. Video and Computer-based Interactive Exercises are Safe and Improve Task-specific Balance in Geriatric and Neurological Rehabilitation: a Randomised Trial. J Physiother 2016;62:20-28. doi: 10.106/j.phys.2015.11.005

209. Fairhall N, Sherrington C, Cameron ID, et al. A Multifactorial Intervention for Frail Older People is More Than Twice as Effective Among Those Who Are Compliant: Complier Average Causal Effect Analysis of a Randomised Trial. J Physiother 2016;63:40-44. doi: 10-1016/j.phys.2016.11.007
210. Hartmann EL, Kitzman D, Rocco M, et al. Physical Function in Older Candidates for Renal Transplantation: An Impaired Population. Clin J Am Soc Nephrol 2009;4(3):588-94. doi: 10.2215/CJN.03860808
211. Oh B, Cho B, Choi HC, et al. The influence of lower-extremity function in elderly individuals' quality of life (QOL): an analysis of the correlation between SPPB and EQ-5D. Arch Gerontol Geriatr 2014;58(2):278-82. doi: 10.1016/j.archger.2013.10.008
212. Treacy D, Hassett L. The Short Physical Performance Battery. J Physiother 2018;64(1):61. doi: 10.1016/j.jphys.2017.04.002
213. Lattanzio F, Corsonello A, Abbatecola AM. Relationship Between Renal Function and Physical Performance in Elderly Hospitalized Patients. Rejuvenation Research 2012;15(6):545-52. doi: 10.1089/rej.2012.1329.
214. Kobau R, Sniezek J, Zack MM, et al. Well-Being Assessment: An Evaluation of Well-Being Scales for Public Health and Population Estimates of Well-Being Among US Adults. Applied Psychology: Health and Wellbeing 2010;2(3):272-97. doi: 10.1111/j.1758-0854.2010.01035.x
215. Diener E, Emmons RA, Larsen RJ, et al. The Satisfaction With Life Scale. J Pers Assess 1985;49(1):71-75.
216. Diener E. Subjective Well-Being. Psychol Bull 1984;95(3):542-45.
217. International Conference on Harmonization. ICH Guideline for Good Clinical Practice - Topic E6: EMA, 2012.
218. WHO. WHO Disability Assessment Schedule 2.0 (WHODAS 2.0) 2018 [Available from: www.who.int/classifications/icf/more_whodas/en/ accessed 07JUL2018].
219. Rand Health. KDQOL Frequently Asked Questions [Available from: www.rand.org/health/surveys_tools/kdqol/faq.html accessed 20SEP2018].
220. Barbosa J, Moura E, Lira C, et al. Quality of Life and Duration of Hemodialysis in Patients with Chronic Kidney Disease (CKD): a Cross-Sectional Study. Fisioter Mov 2017;30(4):781-88. doi: 10.1590/1980-5918.030.004.ao13
221. Ferreira PL, Anes EJ. Medição da Qualidade de Vida de Insuficientes Renais Crónicos: Criação da Versão Portuguesa do KDQOL-SF. Revista Portuguesa de Saúde Pública 2010;28(1):31-39.
222. Likert R. A Technique for the Measurement of Attitudes. Archives of Psychology 1932;22(140):55.
223. Cronbach L. Coefficient Alpha and the Internal Structure of Tests. Psychometrika 1951;16:297-337.
224. DeVellis RF. Scale Development: Theory and Applications. Newbury Park, CA: Sage Publications 1991.
225. Moreira CA, Garletti W, Jr, , Lima LF, et al. Assesment of the Basic Psychometric Properties for the Portuguese Version of the KDQOL-SF. Rev Assoc Med Bras 2009;55(1):22-28.
226. Ferreira JP, Girerd N, Pellicori P, et al. Renal function Estimation and Cockcroft–Gault Formulas for Predicting Cardiovascular Mortality in Population-Based, Cardiovascular Risk, Heart Failure and Post-Myocardial Infarction Cohorts: The Heart 'OMics' in AGEing (HOMAGE) and the High-Risk Myocardial Infarction Database Initiatives. BMC Med 2016;14:181. doi: 10.1186/s12916-016-0731-2
227. Tang H, Ng JH. Googling for a Diagnosis - Use of Google as a Diagnostic Aid: Internet Based Study. BMJ 2006;333:1143-45. doi: 10.1136/bmj.39003.640567
228. Miranda GB, Cordeiro JR, Grinberg M. Patients' Use of the Internet. Arq Bras Cardiol 2014;102(4) doi: 10.5935/abc.20140035
229. Chin JJ. Doctor-patient Relationship: from Medical Paternalism to Enhanced Autonomy. Singapore Med J 2002;43(3):152-55.
230. Botelho RJ. A Negotiation Model for the Doctor- Patient Relationship. Fam Pract 1992;9(2):210-18.
231. Rosland AM, Piette JD. Emerging Models for Mobilizing Family Support for Chronic Disease Management: A Structured Review. Chronic Illness 2010;6(1):7-21. doi: 10.1177/1742395309352254
232. Arestedt L, Persson C, Benzein E. Living as a Family in the Midst of Chronic Illness Scand J Caring Sci 2014;28:29-37. doi: 10.1111/scs.12023
233. Bodenheimer T, Lorig K, Holman H, et al. Patient Self-Management of Chronic Disease in Primary Care. JAMA 2002;288(19):2469-75. doi: 10.1001/jama.288.19.2469

234. Pinheiro J. Empowering Patient Autonomy in Dialysis Patients Via a Doctor-Patient Relationship Model. Port J Nephrol Hypert 2010;24(3):191-93.
235. Hankins DA, Babb AL, Uvelli DA, et al. Creatinine Degradation I: The Kinetics of Creatinine Removal in Patients With Chronic Kidney Disease. Int J Artif Organs 1981;4(1):35-39.
236. Zamora E, Lupón J, Vila J, et al. Estimated Glomerular Filtration Rate and Prognosis in Heart Failure. Value of the Modification of Diet in Renal Disease Study-4, Chronic Kidney Disease Epidemiology Collaboration, and Cockroft-Gault Formulas. J Am Coll Cardiol 2012;59:1709-15. doi: 10.1016/j.jacc.2011.11.06
237. Kontos MC, Jamal SM, Ornato JP, et al. Comparison of the Modification of Diet in Renal Disease and the Cockcroft-Gault Equations for Predicting Mortality in Patients Admitted for Exclusion of Myocardial Ischemia. Am J Cardiol 2008;102(2) doi: 10.1016/j.amjcard.2008.03.023.
238. Szummer K, Lundman P, Jacobson SH, et al. Cockcroft-Gault is Better than the Modification of Diet in Renal Disease Study Fformula at Predicting Outcome after a Myocardial Infarction: Data from the Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies (SWEDEHEART). Am Heart J 2010;159(6):979-86. doi: 10.1016/j.ahj.2010.03.028.
239. Melloni C, Peterson ED, Chen AY, et al. Cockcroft-Gault versus Modification of Diet in Renal Disease: Importance of Glomerular Filtration Rate Formula for Classification of Chronic Kidney Disease in Patients with non-ST-segment Elevation Acute Coronary Syndromes. J Am Coll Cardiol 2008;51(10):991-96. doi: 10.1016/j.jacc.2007.11.045.
240. Ekmekci A, Uluganyan M, Gungor B, et al. Comparison of Cockcroft-Gault and Modification of Diet in Renal Disease Formulas as Predictors of Cardiovascular Outcomes in Patients with Myocardial Infarction Treated with Primary Percutaneous Coronary Intervention. Angiology 2014;65(9):838-43. doi: 10.1177/0003319713505899
241. Food and Drug Administration. Guidance for Industry Pharmacokinetics in Patients with Impaired Renal Function — Study Design, Data Analysis, and Impact on Dosing and Labeling 2010 [Available from: www.fda.gov/downloads/drugs/guidances/ucm204959.pdf accessed 05JUL2018].
242. Anderson JL, Adams CD, Antman EM, et al. ACC/AHA 2007 Guidelines for the Management of Patients With Unstable Angina/Non–ST-Elevation Myocardial Infarction Circulation. 2007. Circulation 2007;116:e148-e304. doi: 10.1161/CIRCULATIONAHA.107.181940
243. Bostom AG, Kronenberg F, Ritz E. Predictive Performance of Renal Function Equations for Patients with Chronic Kidney Disease and Normal Serum Creatinine Levels. J Am Soc Nephrol 2002;13(8):2140-44. doi: 10.1097/01.ASN.0000022011.35035.F3
244. Self I, Lindberg J, Filangeri J, et al. The Healthy Start Renal Clinic: Benefits of Tracking and Early Intervention in Pre-End Stage Renal Disease Patients. The Ochsner Journal 1999;1(4):202-05. doi: 10.1043/1524-5012-1.4.202
245. Van Biesen W, Dequidt C, Vanholder R, et al. The Impact of Healthy Start Peritoneal Dialysis on the Evolution of Residual Renal Function and Nutrition Parameters. Adv Perit Dial 2002;18:44-48.
246. Golper TA. The Rationale for Healthy Start Dialysis. Blood Purif 1999;17:1-9. doi: 10.1159/000014359
247. Abra G, Tamura MK. Timing of Initiation of Dialysis: Time for a New Direction? Curr Opin Nephrol Hypertens 2012;21:329-33. doi: 10.1097/MNH.0b013e328351c244
248. Hsu CY, Bansal N. Measured GFR as "Gold Standard"—All that Glitters Is Not Gold? Clin J Am Soc Nephrol 2011;6:1813-14. doi: doi: 10.2215/CJN.06040611
249. Moura A, Madureira J, Alija P, et al. Predictors of Health-Related Quality of Life Perceived by End-Stage Renal Disease Patients Under Online Hemodiafiltration. Qual Life Res 2015;24(6):1327-35. doi: 10.1007/s11136-014-0854-x
250. Lessan-Pezeshki M, Rostami Z. Contributing Factors in Health-Related Quality of Life Assessment of ESRD Patients: A Single Center Study. Int J Nephrol Urol 2009;1(2):129-36.
251. Cruz MC, Andrade C, Urrutia M, et al. Quality of Life in Patients with Chronic Kidney Disease. Clinics 2011;66(6):991-95. doi: 10.1590/S1807-59322011000600012
252. Domingues D. Validação do WHODAS 2.0 – 12 itens Versão Portuguesa, Aplicada Via Telefone e em Suporte Digital, em Pessoas com 50 ou mais Anos. Aveiro: Departamento de Ciências Médicas, Universidade de Aveiro 2016.

253. Saltycheva M, Bärlundb E, Laimia K. Correlation Between the Pain Numeric Rating Scale and the 12-item WHO Disability Assessment Schedule 2.0 in Patients with Musculoskeletal Pain. Int J Rehabil Res 2018;41(1):87-91. doi: 10.1097/MRR.0000000000000262
254. White MC, Randall K, Alcorn D, et al. Measurement of Patient Reported Disability Using WHODAS 2.0 Before and After Surgical Intervention in Madagascar. BMC Health Serv Res 2018;18:305-. doi: doi.org/10.1186/s12913-018-3112-z
255. Hamid LN, Kobusingye O, Baine SO, et al. Disability Characteristics of Community-Based Rehabilitation Participants in Kayunga District, Ugand. Annals of Global Health 2017;83(3-4):478–88. doi: doi.org/10.1016/j.aogh.2017.10.006
256. Chi WC, Chang KH, Escorpizo R, et al. Measuring Disability and Its Predicting Factors in a Large Database in Taiwan Using the World Health Organization Disability Assessment Schedule 2.0. Int J Environ Res Public Health 2014;11:12148-61. doi: 10.3390/ijerph111212148
257. Reese PP, Cappola AR, Shults J, et al. Physical Performance and Frailty in Chronic Kidney Disease. Am J Nephrol 2013;38:307-15. doi: 10.1159/000355568
258. Freire AN, Guerra RO, Alvarado B, et al. Validity and Reliability of the Short Physical Performance Battery in Two Diverse Older Adult Populations in Quebec and Brazil J Aging Health 2012;24:863. doi: 10.1177/0898264312438551
259. Perera S. Meaningful Change and Responsiveness in Common Physical Performance Measures in Older Adults. J Am Geriatr Soc 2006;54:743-49. doi: 10.1111/j.1532-5415.2006.00701.x
260. Pavot W, Diener E. Understanding SWLS Scores 2013 [Available from: http://labs.psychology.illinois.edu/~ediener/Documents/.
261. Pavot W, Diener E. Review of the Satisfaction With Life Scale. In: Diener E, ed. Assessing Well-Being: The Collected Works of Ed Diener. Nederlands: Springer, Dordrecht 2009.
262. Lucas-Carrasco R, Sastre-Garriga J, Gala I, et al. Preliminary Validation Study of the Spanish Version of the Satisfaction with Life Scale in Persons with Multiple Sclerosis. Disabil Rehabil 2014;36(12):1001-05. doi: 10.3109/09638288.2013.825650
263. Cipora E, Konieczny M, Karwat ID, et al. Satisfaction With Life Among Women with Breast Cancer – Selected Demographic and Social Factors. Ann Agric Environ Med 2018;25(2):314-19. doi: 10.26444/aaem/82622
264. Vázquez C, Duque A, Hervás G. Satisfaction with Life Scale in a Representative Sample of Spanish Adults: Validation and Normative Data. Span J Psychol 2013;16(e82):1-15. doi: 10.1017/sjp.2013.82
265. Rosengren L, Jonasson SB, Brogardh C, et al. Psychometric Properties of the Satisfaction With Life Scale in Parkinson's disease. Acta Neurol Scand 2015;132:164-70. doi: 10.1111/ane.12380
266. Walker SR, Gill K, Macdonald K, et al. Association of Frailty and Physical Function in Patients with Non-Dialysis CKD: a Systematic Review. BMC Nephrol 2013;14(228)
267. Miskulin DC, Abebe KZ, Chapman AB, et al. Health-Related Quality of Life in Patients With Autosomal Dominant Polycystic Kidney Disease and CKD Stages 1–4: A Cross-sectional Study. Am J Kidney Dis 2014;63(2):214-26. doi: 10.1053/j.ajkd.2013.08.017
268. von Korff M, Katon W, Lin E, et al. Potentially Modifiable Factors Associated With Disability Among People With Diabetes. Psychosom Med 2005;67:233-40. doi: 10.1097/01.psy.0000155662.82621.50
269. Pavot W, Diener E. The Satisfaction With Life Scale and the Emerging Construct of Life Satisfaction. The Journal of Positive Psychology 2008;3(2):137-52. doi: 10.1080/17439760701756946
270. Volpato S, Cavalieri M, Sioulis F, et al. Predictive Value of the Short Physical Performance Battery Following Hospitalization in Older Patients. J Gerontol A Biol Sci Med Sci 2011;66(1):89.96. doi: 10.1093/gerona/glq167
271. Guralnik JM, Ferrucci L, Simonsick EM, et al. Lower-Extremity Function in Persons Over the Age of 70 Years as a Predictor of Subsequent Disability N Engl J Med 1995;332(9):556-61. doi: 10.1056/NEJM199503023320902
272. Penninx BW, Ferrucci L, Leveille SG, et al. Lower Extremity Performance in Nondisabled Older Persons as a Predictor of Subsequent Hospitalization. J Gerontol Med Sci 2000;55(11):M691-M97. doi: 10.1093/gerona/55.11.M691
273. Lee YH, Chang KH, Escorpizo R, et al. Accuracy of the World Health Organization Disability Assessment Schedule 2.0 (WHODAS 2.0) Score As an Objective Assessment Tool for Predicting Return-To-Work

Status After Head and Neck Cancer in Male Survivors. Support Care Cancer 2018;1(9) doi: 10.1007/s00520-018-4322-y
274. Mapes DL, Lopes AA, Satayathum S, et al. Health-Related Quality of Life as a Predictor of Mortality and Hospitalization: The Dialysis Outcomes and Practice Patterns Study (DOPPS). Kidney Int 2003;64:339-49. doi: 10.1046/j.1523-1755.2003.00072.x
275. Collins AJ, Roberts TL, St Peter WL, et al. United States Renal Data System Assessment of the Impact of the National Kidney Foundation - Dialysis Outcomes Quality Initiative Guidelines. Am J Kidney Dis 2002;39(4):784-95. doi: 10.1053/ajkd.2002.31999
276. National Kidney Foundation. KDOQI Clinical Practice Guidelines and Clinical Practice. Recommendations for Anemia in Chronic Kidney Disease. Am J Kidney Dis 2006;47:S11-S145. doi: 10.1053/j.ajkd.2006.03.010
277. Hansen R, Chin H, Blalock S, et al. Pre-Dialysis Chronic Kidney Disease: Evaluation of Quality of Life in Clinic Patients Receiving Comprehensive Anemia Care. Res Social Adm Pharm 2009;5(2):143-53. doi: 10.1016/j.sapharm.2008.06.004.
278. Institut Bergonié. Expectations and Priorities of Elderly Patients for a First Medical Treatment for Cancer (PRIORITY) Bordeaux, France, 2018 [Available from: https://clinicaltrials.gov/ct2/show/results/NCT02821793 accessed 18Sep2018].
279. Porter ME, Teisberg EO. How Physicians Can Change the Future of Health Care. JAMA 2007;297(10):1103-11. doi: 10.1001/jama.297.10.1103

Annexes

- Authorization of the Board of the Hospital
- Authorization of the local Ethics Committee
- Authorization of the National Data Protection Commission
- Informed Consent Form
- Initial questionnaire for patients' characterization
- Questionnaire on patients' priorities
- Short Physical Performance Battery form
- World Health Organization Disability Assessment Schedule 2.0 form
- Satisfaction With Life Scale form
- Kidney Disease Quality of Life version 1.3 form

–

Authorization of the Hospital's Administration Board

Authorization of the Local Ethics Commission of the Hospital

Authorization of the National Data Protection Commission

Informed Consent Form

Questionnaire for initial participants characterization

Questionnaire about patients' priorities

Short Physical Performance Battery (SPPB) form

World Health Organization Disability Assessment Schedule (WHODAS) 2.0, 12-itens

Satisfaction With Life Scale (SWLS) form

Kidney Disease Quality of Life (KDQoL), version 1.3 form

Dr.ª Ana Marcos
Diretora Clínica
22.7.2014

Exmo Senhor
Presidente do Conselho de Administração do CHVNGE

Serafim Miguel Guimarães, Assistente Graduado de Nefrologia deste Centro Hospitalar, e aluno do Programa Doutoral em Ciências e Tecnologias da Saúde – Ramo Decisão Médica, da Universidade de Aveiro, vem solicitar a V.Exa. se digne autorizar a recolha de dados para a realização do programa de trabalhos da Tese de Doutoramento, denominado:
"The Clinical Balanced Scorecard: a framework for evaluation of follow-up of chronic patients. The example of Chronic Kidney Disease (CKD)".

Trata-se de uma série de estudos observacionais cujo projeto é apresentado em anexo. Os participantes no estudo serão os doentes renais crónicos seguidos na consulta externa de Nefrologia. O estudo implica apenas a recolha de dados do processo clínico e a aplicação de questionário. Não há qualquer alteração do normal seguimento dos doentes na consulta de Nefrologia nem custos aumentados para o CHVNG/E.

A recolha de dados será feita apenas após a obtenção de consentimento esclarecido escrito por parte dos doente, cujo modelo é também apresentado em anexo. Solicita-se dispensa de obtenção deste consentimento esclarecido para a recolha de resultados de análises clínicas de doentes que já não estejam na consulta de Nefrologia, por morte ou por alta.

A recolha de dados do estudo será submetida a parecer prévio pela Comissão Nacional de Proteção de Dados (CNPD).

Pede deferimento,

VNG, 14 de Maio de 2014

Parecer favorável à autorização do Autor.
10/7/14
CHVNGE, EPE
Dr. Pedro Teixeira
Director UGI Medicina
Nº Mecanográfico: 6071

ANEXOS:
1. Protocolo do estudo
2. Modelo de consentimento esclarecido

CHVNG/E, EPE
Secretariado UGI Medicina
Entrada nº 642
Entrada 27/6/2014
Entrada ___/___/___
Entrada ___/___/___

Secretariado do C.A.
Entrada nº 16137
1ª Entrada 15/5/14
2ª Entrada ___/___/___
3ª Entrada ___/___/___

Authorization of the Hospital's Administration Board

Authorization of the Local Ethics Commission of the Hospital

Authorization of the National Data Protection Commission

Informed Consent Form

Questionnaire for initial participants characterization

Questionnaire about patients' priorities

Short Physical Performance Battery (SPPB) form

World Health Organization Disability Assessment Schedule (WHODAS) 2.0, 12-itens

Satisfaction With Life Scale (SWLS) form

Kidney Disease Quality of Life (KDQoL), version 1.3 form

PARECER

94/2014

" The Clinical Balanced Scorecard : a Framework for evaluation" of follow-up of chronic patients . The example of chronic Kidney Disease

SERVIÇO: Nefrologia

INVESTIGADOR: Serafim Miguel Guimarães

PARECER DA CES emitido na reunião plenária de 05/06/2014

Nada a opor. Cumpre os requisitos éticos necessários à sua aprovação. Aguarda parecer da Comissão Nacional de protecção de dados.

Pode dar parecer aos responsáveis de serviço

Documentos analisados: ofício
Projeto

O Presidente da CES

(Dra. Helena Figueiredo)

CHVNG/E, EPE
Nº 493 / 2014
Data 30 / 4 / 2014
Tipo de documento: Ofício

Remetido ao Secretariado da Comissão de Ética em 05 / 06 / 2014

Serviço de Formação, Ensino e Investigação

Authorization of the Hospital's Administration Board

Authorization of the Local Ethics Commission of the Hospital

Authorization of the National Data Protection Commission

Informed Consent Form

Questionnaire for initial participants characterization

Questionnaire about patients' priorities

Short Physical Performance Battery (SPPB) form

World Health Organization Disability Assessment Schedule (WHODAS) 2.0, 12-itens

Satisfaction With Life Scale (SWLS) form

Kidney Disease Quality of Life (KDQoL), version 1.3 form

COMISSÃO NACIONAL
DE PROTECÇÃO DE DADOS

AUTORIZAÇÃO N.º 5446 /2015

I. Pedido

Serafim Miguel de Sousa Barreto Guimarães, no âmbito de Doutoramento em Ciências e Tecnologias da Saúde – Ramo Decisão Médica, da Universidade de Aveiro, notificou à Comissão Nacional de Proteção de Dados (CNPD) um tratamento de dados pessoais com a finalidade de elaborar um estudo intitulado "O *Balanced Scorecard Clínico*: uma grelha de avaliação do acompanhamento clínico de doentes. O exemplo da Doença renal Crónica."

O objetivo do estudo consiste em elaborar uma escala prognóstica da doença renal crónica, analisando fatores de risco para a sua evolução, bem como a sua expressão a nível clínico e analítico.

O estudo conterá dados dos doentes renais crónicos seguidos em consulta externa de Nefrologia do Centro Hospitalar de Vila Nova de Gaia, a quem será solicitado a assinatura de declaração de consentimento informado para participação no estudo.
O investigador pretende igualmente recolher dados de doentes que tenham falecido devido à doença em estudo, para o que solicitou dispensa de consentimento informado.

Os dados serão recolhidos pelo investigador, num caderno de recolha de dados desenhado especificamente para o estudo, no qual não há identificação nominal dos titulares, sendo aposto um código para o doente. A chave desta codificação só pode ser conhecida do médico/investigador.

Rua de São Bento, 148-3º • 1200-821 LISBOA
Tel: 213 928 400 Fax: 213 976 832
www.cnpd.pt

21 393 00 39
LINHA PRIVACIDADE
Dias úteis das 10 às 13 h

COMISSÃO NACIONAL
DE PROTECÇÃO DE DADOS

Os destinatários são ainda informados sobre a natureza facultativa da sua participação e garantia de confidencialidade no tratamento, caso decidam participar, recolhendo o médico assistente/investigador o seu consentimento informado para o efeito.

Toda a informação em suporte físico será armazenada em local seguro e de acesso reservado e toda a informação em suporte informático será protegida por palavra-passe, do conhecimento apenas do investigador.

II. Análise

A CNPD já se pronunciou na sua Deliberação n.º 227/2007 sobre o enquadramento legal, os fundamentos de legitimidade, os princípios orientadores para o correto cumprimento da LPD, bem como as condições gerais aplicáveis ao tratamento de dados pessoais para a finalidade de estudos de investigação na área da saúde.
Porque em grande parte referentes à vida privada e também à saúde, os dados recolhidos pela requerente têm a natureza de sensíveis, nos termos do disposto no n.º 1 do artigo 7.º da LPD.

Em regra, o tratamento de dados sensíveis é proibido, de acordo com o disposto no n.º 1 do artigo 7.º da LPD. Todavia, nos termos do n.º 2 do mesmo artigo, o tratamento de dados da vida privada e de saúde é permitido, quando haja uma disposição legal que consagre esse tratamento de dados, quando por motivos de interesse público importante o tratamento for indispensável ao exercício das atribuições legais ou estatutárias do seu responsável ou quando o titular dos dados tiver prestado o seu consentimento.

Não estando preenchidas as duas primeiras condições de legitimidade, o fundamento de legitimidade só pode basear-se no consentimento dos titulares dos dados ou dos representantes legais, quando os titulares dos dados sejam incapazes.

Rua de São Bento, 148-3º • 1200-821 LISBOA
Tel: 213 928 400 Fax: 213 976 832
www.cnpd.pt

Assim, é necessário o «consentimento expresso do titular», entendendo-se por consentimento qualquer manifestação de vontade, livre, específica e informada, nos termos da qual o titular aceita que os seus dados sejam objeto de tratamento (cf. artigo 3.º, alínea *h*), da LPD), o qual deve ser obtido através de uma "declaração de consentimento informado" onde seja utilizada uma linguagem clara e acessível.
Nos termos do artigo 10.º da LPD, a declaração de consentimento tem de conter a identificação do responsável pelo tratamento e a finalidade do tratamento, devendo ainda conter informação sobre a existência e as condições do direito de acesso e de retificação por parte do respetivo titular.

O investigador solicitou a dispensa do consentimento informado quanto a doentes que já morreram e dos quais pretende recolher apenas dados analíticos laboratoriais.
De acordo com o entendimento da CNPD versado na referida Deliberação, a dispensa de consentimento informado pressupõe a verificação de dois pressupostos: a impossibilidade de obtenção do consentimento e uma declaração que ateste o interesse público do estudo.

O investigador justificou a impossibilidade de recolha do consentimento informado, alegando que *uma parte do trabalho consiste em avaliar o risco de progressão para doença renal crónica de estádio 5 (...), pelo que era minha intenção aumentar a amostra com dados analíticos de doentes que já morreram ou que já foram colocados em diálise. É virtualmente impossível ir atrás deles. Se apenas tiver os doentes vivos, ainda na fase de pré-diálise, a amostra será ferida de um viés que pode alterar as conclusões. Não há recolha de história clínica, marcadores de infecção, hábitos, apenas de análises de laboratório."*

Não havendo consentimento informado, o fundamento de legitimidade para o tratamento é a execução de missão de interesse público, para o que o investigador juntou declaração do Presidente o Conselho Directivo do Colégio da Especialidade de Nefrologia da Ordem dos Médicos.

Rua de São Bento, 148-3º • 1200-821 LISBOA
Tel: 213 928 400 Fax: 213 976 832
www.cnpd.pt

COMISSÃO NACIONAL
DE PROTECÇÃO DE DADOS

A demonstração da especialidade da situação e a entrega de declaração de interesse público do estudo, requisitos estabelecidos na referida Deliberação, permitem à CNPD autorizar a recolha de dados sem consentimento dos seus titulares.

Quanto aos participantes vivos, de acordo com a declaração de consentimento informado junta aos autos, estão satisfeitas as exigências legais.

Cabe ao Investigador assegurar a confidencialidade dos dados pessoais e da informação tratada, conforme o estatuído na alínea *g*) do artigo 10.º da Lei n.º 21/2014, de 16 de abril (Lei da investigação clínica).

A informação tratada é recolhida de forma lícita (artigo 5.º, n.º1 alínea *a*) da Lei n.º 67/98), para finalidades determinadas, explícitas e legítimas (cf. alínea *b*) do mesmo artigo) e não é excessiva.

III. Conclusão

Em face do exposto, a CNPD autoriza o tratamento de dados pessoais *supra* apreciado, nos termos do n.º 2 do artigo 7.º, da alínea *a*) do n.º 1 do artigo 28.º e do n.º 1 do artigo 30.º da LPD, com as condições e limites fixados na referida Deliberação n.º 227/2007, que se dão aqui por reproduzidos e que fundamentam esta decisão, consignando-se o seguinte:

Responsável pelo tratamento: Serafim Miguel de Sousa Barreto Guimarães;
Finalidade: estudo "O *Balanced Scorecard Clínico*: uma grelha de avaliação do acompanhamento clínico de doentes. O exemplo da Doença renal Crónica."
Categoria de Dados pessoais tratados: código do doente; data do diagnóstico; sexo; idade; história clínica; história familiar de doença renal; datas de consultas hospitalares; altura; peso; pressão arterial; frequência cardíaca; resultados analíticos; questionários de qualidade de vida, de co-morbilidades, de *performance;* hábitos: anti-

Rua de São Bento, 148-3º • 1200-821 LISBOA
Tel: 213 928 400 Fax: 213 976 832
www.cnpd.pt

COMISSÃO NACIONAL
DE PROTECÇÃO DE DADOS

inflamatório, tabaco, ajuste de doses de medicamentos, hábitos alimentares, vacinação, medicação.

Entidades a quem podem ser comunicados: Não há.

Formas de exercício do direito de acesso e rectificação: Junto do investigador.

Interconexões de tratamentos: Não há.

Transferência de dados para países terceiros: Não há;

Prazo de conservação: o código do titular deve ser destruído um mês após o fim do estudo.

Dos termos e condições fixados na Deliberação n.º 227/ 2007 e na presente Autorização decorrem obrigações que o responsável deve cumprir. Deve, igualmente, dar conhecimento dessas condições a todos os intervenientes no circuito de informação.

Lisboa,9 de junho de 2015

Filipa Calvão (Presidente)

Rua de São Bento, 148-3º • 1200-821 LISBOA
Tel: 213 928 400 Fax: 213 976 832
www.cnpd.pt

21 393 00 39
LINHA PRIVACIDADE
Dias úteis das 10 às 13 h

Authorization of the Hospital's Administration Board

Authorization of the Local Ethics Commission of the Hospital

Authorization of the National Data Protection Commission

Informed Consent Form

Questionnaire for initial participants characterization

Questionnaire about patients' priorities

Short Physical Performance Battery (SPPB) form

World Health Organization Disability Assessment Schedule (WHODAS) 2.0, 12-itens

Satisfaction With Life Scale (SWLS) form

Kidney Disease Quality of Life (KDQoL), version 1.3 form

Consentimento Informado para estudo observacional

"O Balanced Scorecard clínico: uma grelha de avaliação do acompanhamento clínica de doentes. O exemplo da Doença Renal Crónica."

Eu, abaixo assinado _____ [nome completo], declaro que

Fui convidado(a) a participar no estudo de investigação clínica acima identificado, o qual tem por objectivo a análise de factores de risco para evolução de doença renal crónica, bem como a sua expressão a nível clínico e analítico.

Foi-me dito que o referido estudo é do tipo observacional, ou seja, em nenhuma fase do estudo vai ser alterada a maneira como o meu médico tem realizado o seu acompanhamento e medicação clínica da minha situação.

Sei que neste estudo também está prevista a realização de um inquérito aos quais devo responder nos dias em que vier ao Centro Hospitalar de Vila Nova de Gaia, para consultas ou realização de exames complementares.

Também sei que os resultados das minhas análises e outros exames complementares vão também ser utilizados para análise neste estudo. Neste particular, foi me garantido que todos os dados relativos à identificação dos participantes neste estudo são confidenciais e que será mantido o anonimato. Os resultados do estudo serão divulgados no meio científico, mas os meus dados pessoais nunca serão apresentados.

Sei que posso recusar-me a participar ou interromper o estudo a qualquer momento, sem nenhum tipo de penalização ou ressentimento pelo meu médico assistente. Também sei que posso, em qualquer altura, requerer ao médico que retire os meus dados da base de dados, ou os corrija, bastando para tal enviar-lhe um email (serafim.guimaraes@chvng.min-saude.pt), telefonar-lhe (telef 927810781) ou falar com ele pessoalmente, no serviço de Nefrologia do Centro Hospitalar de Vila Nova de Gaia.

Compreendi a informação que me foi dada, tive oportunidade de fazer perguntas e as minhas dúvidas foram esclarecidas.

Aceito participar de livre vontade no estudo acima mencionado.

Nome do Participante no estudo _____

Data _____/_____/_____

Assinatura _____

Código de Identificação _____

Declaro ter explicado ao Participante os objectivos e métodos do estudo

Nome do médico investigador responsável.

Data _____/_____/_____

Assinatura _____

Authorization of the Hospital's Administration Board

Authorization of the Local Ethics Commission of the Hospital

Authorization of the National Data Protection Commission

Informed Consent Form

Questionnaire for initial participants characterization

Questionnaire about patients' priorities

Short Physical Performance Battery (SPPB) form

World Health Organization Disability Assessment Schedule (WHODAS) 2.0, 12-itens

Satisfaction With Life Scale (SWLS) form

Kidney Disease Quality of Life (KDQoL), version 1.3 form

universidade de aveiro

Código de identificação:

_____

Questionário de caracterização do participante

Este questionário tem como objetivos recolher os seus dados sociodemográficos. Selecione com um círculo a opção que considera mais adequada ou indique a informação pedida.

Data: ___/___/_____

1. **Sexo**

(1) Feminino (2) Masculino

2. **Data de nascimento**

___/___/_____ (dia/mês/ano)

3. **Nível de escolaridade**

(1) Não tem o 1º ciclo do ensino básico (< 4ª ano, antigo ensino primário)

(2) 1º Ciclo do Ensino Básico (ensino primário, 1ª, 2ª, 3ª e 4ª classe)

(3) 2º Ciclo do Ensino Básico (5º e 6º ano, antigo ciclo preparatório, antigo 1º e 2º ano do liceu)

(4) 3º Ciclo do Ensino Básico (7º, 8º e 9º ano, 9º ano unificado, antigo 3º, 4º e 5º ano do liceu)

(5) Ensino secundário (10º, 11ºe 12º, antigo 2º ciclo do ensino secundário, antigo 6º e 7º ano do liceu/comercial)

(6) Ensino universitário (bacharelato e licenciatura)

(7) Ensino universitário (mestrado, doutoramento, etc.)

4. **Situação laboral**

(1) Ativo

(2) Reformado

5. **Profissão** (se reformado, indicar a profissão anterior):_____

universidade de aveiro

Código de identificação:

_____

6. Rendimento familiar

	Por mês (14 meses)	**Por mês (12 meses)**
(1) Rendimento anual até 7000 euros	Até 500 €	Até 583 €
(2) Rendimento anual superior a 7000 euros e inferior a 20 000 euros	Até 1429 €	Até 1667 €
(3) Rendimento anual superior a 20 000 euros e inferior a 40 000 euros	Até 2857 €	Até 3333 €
(4) Rendimento anual superior a 40 000 e inferior a 80 000 euros	Até 5714 €	Até 6667 €
(5) Rendimento anual superior a 80 000 euros	Mais de 5714 €	Mais de 6667 €

7. Neste momento a prioridade do meu médico deve ser evitar que…

7.1	☐	as **análises piorem**	OU	☐	entre em **diálise**
7.2	☐	tenha que ir ao **serviço de urgência**	OU	☐	que fique **internado**
7.3	☐	**piore e deixe de estar ativo**	OU	☐	que eu **morra**
7.4	☐	as **análises piorem**	OU	☐	tenha que ir ao **serviço de urgência**
7.5	☐	fique **internado**	OU	☐	que eu **morra**
7.6	☐	as **análises piorem**	OU	☐	que fique **internado**
7.7	☐	entre em **diálise**	OU	☐	**piore e deixe de estar ativo**
7.8	☐	tenha que ir ao **serviço de urgência**	OU	☐	que eu **morra**
7.9	☐	**piore e deixe de estar ativo**	OU	☐	que as **análises piorem**
7.10	☐	entre em **diálise**	OU	☐	que fique **internado**
7.11	☐	eu **morra**	OU	☐	que as **análises piorem**
7.12	☐	entre em **diálise**	OU	☐	tenha que ir ao **serviço de urgência**
7.13	☐	tenha que ir ao **serviço de urgência**	OU	☐	**piore e deixe de estar ativo**
7.14	☐	eu **morra**	OU	☐	que entre em **diálise**
7.15	☐	fique **internado**	OU	☐	**piore e deixe de estar ativo**

Authorization of the Hospital's Administration Board

Authorization of the Local Ethics Commission of the Hospital

Authorization of the National Data Protection Commission

Informed Consent Form

Questionnaire for initial participants characterization

Questionnaire about patients' priorities

Short Physical Performance Battery (SPPB) form

World Health Organization Disability Assessment Schedule (WHODAS) 2.0, 12-itens

Satisfaction With Life Scale (SWLS) form

Kidney Disease Quality of Life (KDQoL), version 1.3 form

Código de identificação:

_____

SPPB – Folha de registo

1. **Levantar e sentar de uma cadeira (5 vezes)**
   Completou o teste (seg):_____
   Não completou: _____

Pontuação ordinal do teste de levantar e sentar: _____

0 = não realiza
1 = > 16,7
2 = 16,6 – 13,7 seg
3 = 13,6 - 11,2 seg
4 = < 11,1 seg

2. **Teste do equilíbrio (10 seg)**
   a. Pés juntos: _____
   b. O calcanhar de um pé colocado ao lado do dedo grande do outro pé: _____
   c. Um pé à frente do outro: _____

Pontuação ordinal do teste do equilíbrio: _____

0 = lado a lado 0-9 seg ou não realiza
1 = lado a lado 10, <10 seg com a parte lateral de um calcanhar a tocar nos dedo grande do outro pé.
2 = parte lateral de um calcanhar a tocar nos dedo grande do outro pé 10 seg, um pé à frente do outro 0-2 seg
3 = parte lateral de um calcanhar a tocar nos dedo grande do outro 10 seg, um pé à frente do outro 3-9 seg
4 = um pé à frente do outro 10 seg

3. **Marcha (2,44 metros)**
   a. Completou o teste (seg): _____
   b. Não completou: _____
   c. Ajuda técnica: ☐ Não usou ☐ Usou. Indique qual _____

Pontuação ordinal para a marcha: _____

0 = não faz
1 = >5.7 seg (<0.43 m/seg)
2 = 4.1-5.6 seg (0.44-0.60 m/seg)
3 = 3.2-4.0 (0.61-0.77 m/seg)
4 = <3.1 seg (>0.78 m/seg)

Pontuação ordinal final: _____

Amplitude: 0 (pior performance) a 12 (melhor performance).

Authorization of the Hospital's Administration Board

Authorization of the Local Ethics Commission of the Hospital

Authorization of the National Data Protection Commission

Informed Consent Form

Questionnaire for initial participants characterization

Questionnaire about patients' priorities

Short Physical Performance Battery (SPPB) form

World Health Organization Disability Assessment Schedule (WHODAS) 2.0, 12-itens

Satisfaction With Life Scale (SWLS) form

Kidney Disease Quality of Life (KDQoL), version 1.3 form

universidade de aveiro

Código de identificação:

_____

Versão Portuguesa da WHODAS 2.0 12 itens

As questões seguintes são acercadas dificuldades que sentiu devido à sua condição de saúde. Condições de saúde incluem doenças, problemas de saúde de curta ou longa duração, lesões, problemas mentais ou emocionais, ou problemas relacionados com álcool ou drogas.

As suas respostas só devem refletir os últimos 30 dias e responda às questões pensando em quanta dificuldade teve em realizar as seguintes atividades.

Nos últimos 30 dias, quanta dificuldade teve em:		Nenhuma	Ligeira	Moderada	Grave	Completa / Não faz
S1	Ficar de pé por longos períodos, como 30 minutos?	1	2	3	4	5
S2	Tratar das suas responsabilidades domésticas?	1	2	3	4	5
S3	Aprender uma nova tarefa, por exemplo, aprender o caminho para um novo lugar?	1	2	3	4	5
S4	Quanta dificuldade que teve em participar em atividades na comunidade (como por exemplo, festivais, religiosas ou outras) da mesma forma que qualquer outra pessoa?	1	2	3	4	5
S5	Quanto se sentiu emocionalmente afetado pela sua condição de saúde? *	1	2	3	4	5

* Codificação: Nada | Ligeiramente | Moderadamente | Gravemente |Completamente

universidade de aveiro

Código de identificação:

_____

Nos últimos 30 dias, quanta dificuldade teve em:		Nenhuma	Ligeira	Moderada	Grave	Completa / Não faz
S6	Concentrar-se a fazer algo durante dez minutos?	1	2	3	4	5
S7	Andar uma distância longa como um quilómetro [ou equivalente]?	1	2	3	4	5
S8	Lavar todo o corpo?	1	2	3	4	5
S9	Vestir-se?	1	2	3	4	5
S10	Lidar com pessoas que não conhece?	1	2	3	4	5
S11	Manter uma amizade?	1	2	3	4	5
S12	No seu trabalho/escola do dia-a-dia?	1	2	3	4	5

H1	Globalmente, nos últimos 30 dias, quantos dias estiveram presentes estas dificuldades?	Registe o número de dias __
H2	Nos últimos 30 dias, em quantos dias esteve totalmente impossibilitado de realizar as suas atividades habituais ou de trabalhar devido à sua condição de saúde?	Registe o número de dias __
H3	Nos últimos 30 dias, sem contar os dias em que esteve totalmente impossibilitado, em quantos dias diminuiu ou reduziu as suas atividades habituais ou de trabalho devido à sua condição de saúde?	Registe o número de dias __

Authorization of the Hospital's Administration Board

Authorization of the Local Ethics Commission of the Hospital

Authorization of the National Data Protection Commission

Informed Consent Form

Questionnaire for initial participants characterization

Questionnaire about patients' priorities

Short Physical Performance Battery (SPPB) form

World Health Organization Disability Assessment Schedule (WHODAS) 2.0, 12-itens

Satisfaction With Life Scale (SWLS) form

Kidney Disease Quality of Life (KDQoL), version 1.3 form

universidade de aveiro

Código de identificação:

_____

SWLS – SATISFACTION WITH LIFE SCALE

Encontra-se a seguir cinco afirmações com as quais pode concordar ou discordar. Utilizando a escala de 1 a 7 refira o seu grau de acordo com cada item colocando um círculo no número que corresponde à sua resposta. Procure ser sincero nas suas respostas.

1 – discordo totalmente
2 – discordo
3 – discordo ligeiramente
4 – nem concordo, nem discordo
5 – concordo ligeiramente
6 – concordo
7 – concordo totalmente

1.	Em muitos aspetos, a minha vida aproxima-se dos meus ideais.	1 2 3 4 5 6 7
2.	As minhas condições de vida são excelentes.	1 2 3 4 5 6 7
3.	Estou satisfeito com a minha vida.	1 2 3 4 5 6 7
4.	Até agora, consegui obter aquilo que era importante na vida.	1 2 3 4 5 6 7
5.	Se pudesse viver a minha vida de novo, não alteraria praticamente nada.	1 2 3 4 5 6 7

Total: _____

Score:

30-35 Totalmente satisfeito
25-29 Satisfeito
20-24 Mais ou menos satisfeito
15-19 Um pouco insatisfeito
10-14 Insatisfeito
5-9 Totalmente insatisfeito

Authorization of the Hospital's Administration Board

Authorization of the Local Ethics Commission of the Hospital

Authorization of the National Data Protection Commission

Informed Consent Form

Questionnaire for initial participants characterization

Questionnaire about patients' priorities

Short Physical Performance Battery (SPPB) form

World Health Organization Disability Assessment Schedule (WHODAS) 2.0, 12-itens

Satisfaction With Life Scale (SWLS) form

Kidney Disease Quality of Life (KDQoL), version 1.3 form

A sua saúde

– e –

o seu bem-estar

Doença Renal e Qualidade de Vida (KDQOL-SF™ 1.3)

O presente estudo pretende saber como olha para a sua saúde. Estas informações dar-nos-ão a conhecer a forma como se sente e qual a sua capacidade para desempenhar as actividades do seu dia-a-dia.

Obrigado por responder a estas perguntas!

ESTUDO DA QUALIDADE DE VIDA PARA DOENTES EM DIÁLISE

Qual é o objectivo do estudo?

Este estudo tem contado com a colaboração de médicos e doentes. O objectivo é avaliar a qualidade de vida dos doentes com doença renal.

O que terei de fazer?

Para este estudo, queríamos que respondesse hoje a um inquérito sobre a sua saúde, como se sente e os seus dados pessoais.

Confidencialidade das informações?

Não lhe pedimos o nome. As suas respostas serão misturadas com as de outros participantes nas conclusões do estudo. Qualquer informação que permita a sua identificação será encarada como estritamente confidencial. Além disso, todas as informações recolhidas serão apenas usadas para a finalidade deste estudo e não serão reveladas ou disponibilizadas para qualquer outra finalidade sem a sua autorização prévia.

De que modo é que a minha participação me poderá beneficiar?

As informações que prestar dir-nos-ão o que pensa dos cuidados e dar-nos--ão uma compreensão adicional sobre os efeitos dos cuidados médicos na saúde dos doentes. Estas informações ajudarão a avaliar os cuidados prestados.

Tenho que participar?

Não é obrigado/a a preencher o inquérito e pode recusar-se a responder a qualquer pergunta. A sua decisão de participar não vai afectar os cuidados médicos que irá receber.

A sua saúde

Este questionário inclui uma ampla variedade de perguntas sobre a sua saúde e a sua vida. Estamos interessados em saber como se sente em relação a cada um destes assuntos.

1. Em geral, diria que a sua saúde é: [Marque um ☒ no quadrado que melhor descreve a sua saúde.]

Excelente	Muito Boa	Boa	Razoável	Fraca
∇	∇	∇	∇	∇
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. <u>Comparando com o que acontecia há um ano</u>, como descreve o seu estado geral <u>actual</u>?

Muito melhor agora do que há um ano atrás	Um pouco melhor agora do que há um ano atrás	Aproxima-damente igual há um ano atrás	Um pouco pior agora do que há um ano atrás	Muito pior agora do que há um ano atrás
∇	∇	∇	∇	∇
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

3. As perguntas que se seguem são sobre actividades que executa no seu dia-a-dia. Será que a sua saúde o/a limita nestas actividades? Se sim, quanto? [Marque um ☒ em cada linha.]

		Sim, muito limitado/a ∇	Sim, um pouco limitado/a ∇	Não, nada limitado/a ∇
a	Actividades violentas, tais como correr, levantar pesos, participar em desportos extenuantes	☐ 1	☐ 2	☐ 3
b	Actividades moderadas, tais como deslocar uma mesa ou aspirar a casa	☐ 1	☐ 2	☐ 3
c	Levantar ou pegar nas compras de mercearia	☐ 1	☐ 2	☐ 3
d	Subir vários lanços de escada	☐ 1	☐ 2	☐ 3
e	Subir um lanço de escadas	☐ 1	☐ 2	☐ 3
f	Inclinar-se, ajoelhar-se ou baixar-se	☐ 1	☐ 2	☐ 3
g	Andar mais de 1 Km	☐ 1	☐ 2	☐ 3
h	Andar várias centenas de metros .	☐ 1	☐ 2	☐ 3
i	Andar uma centena de metros ...	☐ 1	☐ 2	☐ 3
j	Tomar banho ou vestir-se sozinho/a	☐ 1	☐ 2	☐ 3

4. Durante as últimas 4 semanas teve, no seu trabalho ou actividades diárias, algum dos problemas apresentados a seguir como consequência do seu estado de saúde físico?

Quanto tempo, nas últimas quatro semanas	Sempre	A maior parte do tempo	Algum tempo	Pouco tempo	Nunca
	∇	∇	∇	∇	∇
a Diminuiu o **tempo gasto** a trabalhar ou noutras actividades?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Fez **menos** do que queria?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Sentiu-se limitado/a no **tipo** de trabalho ou outras actividades?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Teve **dificuldade** em executar o seu trabalho ou outras actividades (por exemplo, foi preciso mais esforço?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

5. Durante as últimas 4 semanas, teve com o seu trabalho ou com as suas actividades diárias, algum dos problemas apresentados a seguir devido a quaisquer problemas emocionais (tal como sentir-se deprimido/a ou ansioso/a)?

Quanto tempo, nas últimas quatro semanas	Sempre	A maior parte do tempo	Algum tempo	Pouco tempo	Nunca
	∇	∇	∇	∇	∇
a Diminuiu o **tempo gasto** a trabalhar ou noutras actividades?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Fez **menos** do que queria?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Executou o seu trabalho ou outras actividades **menos cuidadosamente** do que era costume	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

6. Durante as últimas 4 semanas, em que medida é que a sua saúde física ou problemas emocionais interferiram no seu relacionamento social normal com a família, amigos, vizinhos ou outras pessoas?

Nada	Um pouco	Moderadamente	Bastante	Imenso
∇	∇	∇	∇	∇
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

7. Durante as últimas 4 semanas teve dores?

Nenhumas	Muito fracas	Ligeiras	Moderadas	Fortes	Muito fortes
∇	∇	∇	∇	∇	∇
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

8. Durante as últimas 4 semanas, de que forma é que a dor interferiu com o seu trabalho normal (tanto o trabalho fora de casa como o trabalho doméstico)?

Nada	Um pouco	Moderadamente	Bastante	Imenso
∇	∇	∇	∇	∇
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

9. As perguntas que se seguem pretendem avaliar a forma como se sentiu e como lhe correram as coisas nas últimas quatro semanas.

Para cada pergunta, coloque por favor um círculo à volta do número que melhor descreve a forma como se sentiu.

Certifique-se que coloca um círculo em cada linha.

Quanto tempo, nas últimas quatro semanas	Sempre	A maior parte do tempo	Algum tempo	Pouco tempo	Nunca
	∇	∇	∇	∇	∇
a Se sentiu cheio/a de vitalidade?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Se sentiu muito nervoso/a? ...	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Se sentiu tão deprimido/a que nada o/a animava?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Se sentiu calmo/a e tranquilo/a?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
e Se sentiu com muita energia?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
f Se sentiu deprimido/a?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
g Se sentiu estafado/a?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
h Se sentiu feliz?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
i Se sentiu cansado/a?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

10. Durante as últimas quatro semanas, até que ponto é que a sua saúde física ou problemas emocionais limitaram a sua actividade social (tal como visitar amigos ou familiares próximos)?

Sempre	A maior parte do tempo	Algum tempo	Pouco tempo	Nunca
∇	∇	∇	∇	∇
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

11. Por favor, diga em que medida são verdadeiras ou falsas as seguintes afirmações.

		Absolutamente verdade	Verdade	Não sei	Falso	Absolutamente falso
		∇	∇	∇	∇	∇
a	Parece que adoeço mais facilmente do que os outros ...	☐ 1	☐ 2	☐ 3 ...	☐ 4	☐ 5
b	Sou tão saudável como qualquer outra pessoa	☐ 1	☐ 2	☐ 3 ...	☐ 4	☐ 5
c	Estou convencido/a que a minha saúde vai piorar	☐ 1	☐ 2	☐ 3 ...	☐ 4	☐ 5
d	A minha saúde é óptima.....	☐ 1	☐ 2	☐ 3 ...	☐ 4	☐ 5

A sua doença renal

12. Até que ponto é que cada uma das seguintes afirmações é verdadeira ou falsa para si?

		Completa-mente verdadeira	Quase toda verdadeira	Não sei	Quase toda falsa	Completa-mente falsa
a	A minha doença renal interfere demasiado na minha vida	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b	Passo demasiado tempo a tratar da minha doença renal .	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c	Sinto-me desanimado/a com a minha doença renal ...	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d	Sinto-me um peso para a minha família .	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

13. Estas perguntas são sobre como se sente e como têm corrido as últimas 4 semanas. Para cada pergunta, dê a resposta que mais se aproxima da forma como se tem sentido.

Quantas vezes nas últimas 4 semanas …

		Nunca	Poucas vezes	Algumas vezes	Bastantes vezes	Quase sempre	Sempre
a	se isolou das outras pessoas à sua volta?	∇	∇	∇	∇	∇	∇
b	demorou a reagir a coisas que foram ditas ou feitas?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
c	se mostrou irritável com os que o/a rodeiavam?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
d	teve dificuldades em se concentrar ou pensar?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
e	se deu bem com as outras pessoas?.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
f	se sentiu confuso/a?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

14. Nas últimas 4 semanas, até que ponto se sentiu incomodado/a por cada uma das seguintes situações?

	Nada incomodado	Um pouco incomodado	Moderada-mente incomodado	Muito incomodado	Extrema-mente incomodado
	∇	∇	∇	∇	∇
A Dores musculares?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Dor no peito?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Cãibras?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Comichão?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
e Pele sêca?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
f Falta de ar?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
g Sensação de desmaio e tonturas?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
h Falta de apetite? .	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
i Esgotado/a ou sem forças?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
j Mãos ou pés dormentes?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
k Náusea ou indisposição	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
l (Apenas para doentes em hemodiálise) Problemas com a fístula?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
m (Apenas para doentes em diálise peritoneal) Problemas com seu catéter?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Efeitos da doença renal no seu dia-a-dia

15. Algumas pessoas sentem-se incomodadas com os efeitos da doença renal no seu dia-a-dia, enquanto outras não. Até que ponto é que a doença renal o/a incomoda em cada uma das seguintes áreas?

	Nada incomodado	Um pouco incomodado	Moderada-mente incomodado	Muito incomodado	Extrema-mente incomodado
	∇	∇	∇	∇	∇
a Restrição de líquidos?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Restrição dietética?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Capacidade para fazer os trabalhos domésticos?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Capacidade para viajar?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
e Dependência de médicos e outro pessoal clínico?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
f Stresse ou preocupações causadas pela doença renal?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
g Vida sexual?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
h Aparência física?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

As três perguntas que se seguem são pessoais e dizem respeito à sua actividade sexual, mas as suas respostas são importantes para compreendermos de que forma é que a doença renal interfere na vida das pessoas.

16. Teve actividade sexual nas últimas 4 semanas?

(Faça um círculo à volta de um número)

Não ..... 1 → Se respondeu não, por favor salte para a Pergunta 17

Sim 2

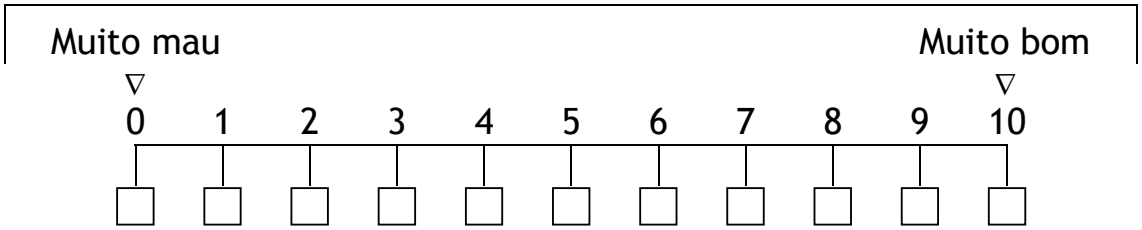
Até que ponto cada uma das seguintes situações constituiu um problema nas últimas 4 semanas

	Sem problema	Um pequeno problema	Algum problema	Um grande problema	Um problema grave
	∇	∇	∇	∇	∇
a Ter prazer sexual?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Ficar excitado/a sexualmente?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

17. Para a pergunta seguinte, classifique o seu sono usando uma escala de 0 a 10 em que 0 representa "muito mau" e 10 "muito bom".

Se acha que o seu sono fica entre o "muito mau" e o "muito bom", faça uma cruz no quadrado por baixo do número 5. Se acha que o seu sono é um nível melhor do que 5, faça uma cruz no quadrado por baixo de 6. Se acha que o seu sono é um nível pior do que 5, faça uma cruz no quadrado por baixo do 4 (e assim por diante).

Numa escala de 0 a 10, como classificaria o seu sono em geral? [Faça uma cruz no quadrado.]



18. Com que frequência é que nas últimas 4 semanas...

		Nunca	Poucas vezes	Algumas vezes	Bastantes vezes	Quase sempre	Sempre
		∇	∇	∇	∇	∇	∇
a	acordou durante a noite e teve dificuldades em voltar a adormecer?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
b	dormiu o tempo suficiente?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
c	teve dificuldade em se manter acordado/a durante o dia?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

19. Relativamente à sua família e aos seus amigos, qual o seu grau de satisfação com...

		Muito insatisfeito	Um pouco insatisfeito	Um pouco satisfeito	Muito satisfeito
		∇	∇	∇	∇
a	a quantidade de tempo que consegue passar com a família e com os amigos?	☐ 1	☐ 2	☐ 3	☐ 4
b	o apoio que recebe da família e dos amigos?	☐ 1	☐ 2	☐ 3	☐ 4

20. Nas últimas 4 semanas, teve um trabalho remunerado?

Sim	Não
∇	∇
☐ 1	☐ 2

21. A sua saúde impossibilita-o/a de ter um trabalho remunerado?

Sim	Não
∇	∇
☐ 1	☐ 2

22. Em geral, como classificaria a sua saúde?

A pior possível (tão má ou pior do que estar morto/a)	Nem muito boa nem muito má	A melhor possível

∇					∇					∇
0	1	2	3	4	5	6	7	8	9	10
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

Satisfação com os cuidados prestados

23. Pense nos cuidados que recebe na diálise renal. Em termos da sua satisfação, como classificaria a amabilidade e o interesse que tiveram consigo como pessoa?

Muito mau	Mau	Suficiente	Bom	Muito bom	Excelente	O melhor possível
∇	∇	∇	∇	∇	∇	∇
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7

24. Até que ponto é que cada uma das seguintes afirmações é verdadeira ou falsa?

		Completa-mente verdadeira	Quase toda verdadeira	Não sei	Quase toda falsa	Completa-mente falsa
		∇	∇	∇	∇	∇
a	O pessoal da diálise incita-me a ser tão independente quanto possível .	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b	O pessoal da diálise ajuda-me a lidar com a minha doença renal	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Obrigado por responder a estas perguntas!

2012-2018
@Matosinhos, Porto & Aveiro