Standardised Outcomes in Nephrology – Chronic Kidney Disease (SONG-CKD): establishing a core outcome set in chronic kidney disease

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A thesis submitted in fulfilment of the requirements for the degree of Doctor of Philosophy

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Declaration

This is to certify that to the best of my knowledge, the content of this thesis is my own work. This thesis has not been submitted for any degree or other purposes.

I certify that the intellectual. content of this thesis is the product of my own work and that all the assistance received in preparing this thesis and sources has been acknowledged.

Signature…… Date: 31st March 2025

Andrea Beatriz Matus González

Author's Contribution

The work presented in this thesis has been carried out by the author under the supervision of Professor Allison Jaure of the Sydney School of Public Health, The University of Sydney and Professor Armando Teixeira-Pinto of the Sydney School of Public Health, The University of Sydney.

The author planned the research, designed the studies, obtained ethics approval, collected, managed and analysed the data, interpreted results, drafted and revised the manuscripts for submission to peer-reviewed journals, and wrote and compiled this thesis.

As supervisor for the candidature upon which this thesis is based, I can confirm that the authorship attribution statements above are correct.

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Professor Allison Jaure

Ethical Clearance

The study presented in Chapter 2, 3, 4, 5 and 6 received ethics approval by the Ethics Committee of the University of Sydney (2019-899).

All participants gave written informed consent for participation in these studies.

Abstract

The global median prevalence of chronic kidney disease (CKD) is estimated to be 9.5%. Patients with CKD have an increased risk of progression to kidney failure requiring kidney replacement therapy in the form of dialysis or kidney transplant, life-threatening comorbidities, and impaired quality of life. Advances in care and outcomes may be limited, in part, by problems with the selection and reporting of outcomes in trials in CKD. The aim of the Standardised Outcomes in Nephrology – Chronic Kidney Disease (SONG-CKD) project is to establish a core outcome set for trials in adults with chronic kidney disease not yet requiring kidney replacement therapy. The core outcomes set will be based on the shared priorities of patients, caregivers, and health professionals. This will help to ensure that trials include outcomes that are of critical importance to all stakeholders to support shared decision-making.

The SONG-CKD projects included in this these are: focus groups with nominal group technique to identify and rank patient-important outcomes; interviews with clinicians in caring for patients with CKD; an international two-round Delphi survey to develop consensus among patients and caregivers to identify, rank, and describe reasons for their choice of outcomes; and two stakeholder workshops (in English and Spanish) to discuss and endorse the proposed core outcomes. The thesis also includes the report of the SONG-CKD Life participation workshop as this outcome was identified as a core patient-reported outcome. The SONG-CKD core outcome set will ultimately improve the evidence base for shared decision-making regarding treatment among patients, caregivers, and health professionals.

Acknowledgements

This thesis reflects the immense support from many remarkable individuals, for which I am deeply grateful.

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A big thank you to all the amazing patients, family members, and caregivers. Your time, expertise, and emotional support have made such a difference in this work. I hope that seeing your voices represented here helps you understand just how valuable and impactful your contributions truly are. We couldn't have done it without you.

I count myself blessed to have a beloved family. To my husband Javier, who supported me daily with my lovely baby Clemente, you both shared in every joy and frustration, offering unwavering patience and support. I am here pursuing my dreams because of you both. I am profoundly indebted to my sister, Daniela, for always shouldering all my responsibilities with unlimited kindness and generosity when I needed her. To my parents, who always believed in my abilities, thank you for giving me the courage to dream and embark on this life-changing journey. Your love, help and absolute faith in me have been my guiding light. Together, you form the foundation of my strength and resilience. I am genuinely grateful for the invaluable lessons I continue to learn from each of you.

This thesis is dedicated to all people with living with chronic illness and their families and to my soon Clemente – to inspiring me to look at life with from another perspective.

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First Author Publications Arising from this Thesis

This thesis is presented for examination as a thesis containing published work. Chapters 2, 3, 4 and 5 have been published in international peer-reviewed journals. Chapter 6 has been submitted for publication. The candidate is the first and corresponding author on all of these papers.

Chapter 2

Matus González A, Gutman T, Lopez-Vargas P, Anumudu S, Arce CM, Craig JC, Dunn L, Eckardt KU, Harris T, Levey AS, Lightstone L, Scholes-Robertson N, Shen JI, Teixeira-Pinto A, Wheeler DC, White D, Wilkie M, Jadoul M, Winkelmayer WC, Tong A. Patient and Caregiver Priorities for Outcomes in CKD: A Multinational Nominal Group Technique Study. Am J Kidney Dis. 2020 Nov;76(5):679-689.

Chapter 3

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a multinational Delphi survey involving patients, caregivers and health professionals. Nephrol Dial Transplant. 2024 Jul 31;39(8):1310-1321

Chapter 5

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Chapter 6

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Conference Proceedings Arising from this Thesis

2021

Matus Gonzalez A, on behalf of the workshop investigators. Standardised Outcomes in Nephrology- Chronic Kidney Disease (SONG-CKD) Outcomes for clinical trials involving adults with chronic kidney disease: a multinational Delphi survey involving patients, caregivers and health professionals. Congreso Chileno de Nefrología Modalidad Online, 15-19 November 2021. Santiago of Chile.

2023

Matus Gonzalez A, on behalf of the workshop investigators. Patient-centred Outcomes and Core Outcome Set for CKD What matters to patients and caregivers? SONG-CKD. Conference talk in 2023 Dialysis, Nephrology and Transplantation Workshop-Noosa. Sunday 26th March 2023. Noosa Australia.

2024

Matus Gonzalez A, on behalf of the workshop investigators. Outcomes for clinical trials involving adults with chronic kidney disease: a multinational Delphi survey involving patients, caregivers and health professionals. Conference poster presentations World Congress of Nephrology International Society of Nephrology 2024-Buenos Aires Argentina. Sunday 14th April 2024. Buenos Aires Argentina.

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Matus Gonzalez A, on behalf of the workshop investigators. Outcomes for clinical trials involving adults with chronic kidney disease: a multinational Delphi survey involving patients, caregivers and health professionals. Conference presentation 59th ANZSN ASM being held at the Adelaide Convention Centre. Tuesday 3rd September 2024. Adelaide, Australia.

Matus Gonzalez A, on behalf of the workshop investigators. A core outcome set for trials in chronic kidney disease: report of the Standardized Outcomes in Nephrology – chronic kidney disease (SONG-CKD) stakeholder workshops. Conference presentation 59th ANZSN ASM being held at the Adelaide Convention Centre. Tuesday 3rd September 2024. Adelaide, Australia.

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List of Abbreviations

ACR	Albumin-to-creatinine ratio
AER	Albumin excretion rate
ANZDATA	Australian and New Zealand Dialysis and Transplant
BWS	Best-Worst Scale
Ca	Calcium
CKD	Chronic kidney disease
CKD-FIX	Controlled trial of slowing of kidney disease progression From the Inhibition of Xanthine oxidase
COMET	Core Outcome Measures in Effectiveness
COREQ	Consolidated Criteria for Reporting Qualitative Studies
COS-STAD	Core Outcome Set-STAndards for Development
COVID-19	SARS-CoV-2
CREDENCE	Evaluation of the Effects of Canagliflozin on Renal and Cardiovascular Outcomes in Participants with Diabetic Nephropathy
CVD	Cardiovascular disease
DASH	Dietary Approaches to Stop Hypertension
EMA	European Medicines Agency
ESKD	End-stage kidney disease
FDA	United States Food and Drug Administration
GFR	Glomerular filtration rate
GLP-1 RA	Glucagon-like peptide-1 receptor agonists
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HD	hemodialysis
IS	Importance score
ISN	International Society of Nephrology
ISRCTN	The International Standard Randomized Controlled Trial Number
KDIGO	Kidney Disease Improving Global Outcomes
KRT	Kidney replacement therapy
LP	Life participation

METs	Metabolic equivalents
MRA	Mineralocorticoid receptor antagonists
OMERACT	Outcome Measures in Rheumatology
PHOS	Phosphate
PPE	Personal protective equipment
PTH	Parathyroid hormone
SGLT2i	Sodium-glucose cotransporter-2 inhibitors
SLANH	Sociedad latinoamericana de nefrología e hipertensión
SONAR	Study Of Diabetic Nephropathy with Atrasentan
SONG	Standardised Outcomes in Nephrology
WHO	World Health Organization

Chapter 1: Introduction

1.1 Overview

> *"I'm really keen on living well. What will really help me to live well and to feel well? That will guide my treatment decision-making."* - Patient with chronic kidney disease

This thesis is presented as a series of chapters that address the overall aim of establishing a core outcomes set for research in patients with chronic kidney disease (CKD) who do not yet require kidney replacement therapy in the form of dialysis or kidney transplantation. In this chapter, I will provide an overview of the definition, classification and epidemiology of CKD, quality of life and symptoms in patients with CKD, management of CKD and the need for a core outcomes set for trials in CKD. This chapter also includes the rationale for my research and an outline of the aims of each study included in this thesis. Some sections of this chapter have been taken from a published protocol[1] and supplemented with additional information.

1.2 Definition, classification and epidemiology of CKD

Definition of CKD

Chronic kidney disease (CKD) is defined as abnormalities of kidney structure or function, present for greater than three months.[2] The markers of kidney damage can include one or more of the following: albuminuria (albumin-to-creatinine ratio (ACR) $\geq$30 mg/g [$\geq$3 mg/mmol]), urine sediment abnormalities, persistent haematuria, electrolyte and other abnormalities due to tubular disorders, abnormalities detected by histology, structural

abnormalities detected by imaging, history of kidney transplantation, and a glomerular filtration rate (GFR) of less than 60 ml/min per 1.73 m^2.

Classification of CKD

According to the Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guidelines, CKD is classified based on i) cause, ii) GFR category (G1–G5), and iii) albuminuria category (A1–A3), abbreviated as CGA.[2] These three components are required to make an assessment in patients with CKD in terms of disease severity and risk. The definition of CKD includes multiple markers of kidney damage, not just decreased GFR and albumin-to-creatinine ratio (ACR) >30 mg/g [>3 mg/mmol], and the classification system for CKD is based on of GFR and degree of albuminuria.[3] (Table 1.1 and 1.2)

Table 1.1 Stages of CKD based on GFR categories[3]

GFR category	**GFR (ml/min per 1.73 m^2)**	**Terms**
G1	≥90	Normal or high
G2	60–89	Mildly decreased(a)
G3a	45–59	Mildly to moderately decreased
G3b	30–44	Moderately to severely decreased
G4	15–29	Severely decreased
G5	<15	Kidney failure

CKD, chronic kidney disease; GFR, glomerular filtration rate. (a) Relative to the young adult level. In the absence of evidence of kidney damage, neither G1 nor G2 fulfills the criteria for CKD.

Table 1.2 Albuminuria categories in chronic kidney disease[3]

		ACR (approximately equivalent)		
Category	**AER (mg/24 h)**	**(mg/mmol)**	**(mg/g)**	**Terms**
A1	<30	<3	<30	Normal to mildly increased
A2	30-300	30-300	30-300	Moderately increased(a)
A3	>300	>30	>300	Severely increased

ACR, albumin-to-creatinine ratio; AER, albumin excretion rate. a Relative to the young adult level.

Epidemiology

CKD is global public health problem that affects over 850 million people worldwide, and is among the top ten contributors to mortality.[4] Based on recent data from the International Society of Nephrology Global Kidney Health atlas, the global median prevalence of CKD was 9.5% in 2024.[5] The burden of CKD is higher in low-socioeconomic-index regions, such as Central Sub-Saharan Africa and Central Latin America.[6]

Diabetes mellitus and hypertension are the most common causes of CKD in adults.[7] More than one third of patients with type 2 diabetes mellitus have CKD.[8] Other causes of CKD include but are not limited to glomerular disease, polycystic kidney disease, infection, drug toxicity, autoimmune disorders, and renal artery stenosis.

Patients with CKD prior to the need for kidney replacement therapy have an increased risk of mortality and life-threatening comorbidities including cardiovascular disease, and hospitalisation.[9] CKD can progress to kidney failure requiring kidney replacement therapy,

with the number of patients requiring a kidney transplant or dialysis exceeding four million worldwide.[10, 11]

1.3 Quality of life and symptoms in patients with CKD

Quality of life

Patients across all stages of CKD have lower quality of life compared with the general population.[12] In general, quality of life has been found to decline as CKD progresses,[13] which may related to the increased burden of symptoms and risk of comorbidities and hospitalisation.[12, 14, 15] Studies have shown that the determinants of poor health-related quality of life in patients with CKD include comorbidities such as cardiovascular disease, anxiety and depression, as well as socio-demographic factors including unemployment, female gender, and older age.[16]

Symptoms

Patients with CKD experience many symptoms that can be severe and debilitating and impair functioning and overall well-being.[17] These symptoms include but are not limited to fatigue, pain, poor sleep, sexual dysfunction, pruritis, heartburn, cramps, oedema, decreased appetite, and dyspnoea.[18, 19] While CKD is often asymptomatic in earlier stages, as kidney disease progresses, patients may experience an increased symptom burden, particularly those related to uraemia.[20]

1.4 Management of CKD

According to the KDIGO clinical practice guidelines for CKD, managing the risk factors of disease progression, such as hypertension, anaemia, dyslipidaemia, mineral bone disorder, potassium disorder, and severe acidosis, can significantly reduce the risk of progression of CKD and subsequent kidney failure.[3] There is also a need to minimise the risk of or manage comorbidities and complications that are common in the CKD population, including cardiovascular disease, diabetes, and infections. In general, the management of patients with CKD often involves pharmacological management of blood pressure and glycaemic control, and lifestyle modification (e.g. reducing dietary sodium and protein intake), to minimise the risk of CKD progression and its associated complications. In the following section, I will outline the main pharmacological and lifestyle management strategies for patients with CKD.

Pharmacological management

The pharmacological management strategy for patients with CKD is generally focussed in reducing the risk of disease progression and complications. Renin-angiotensin system inhibitors may be prescribed to slow the progression of CKD progression and to control blood pressure.[21, 22] Sodium-glucose cotransporter-2 inhibitors (SGLT2i) are generally recommended to manage patients with CKD regardless of diabetes status.[21] Mineralocorticoid receptor antagonists (MRA) may reduce blood pressure and albuminuria in people with CKD.[21] Glucagon-like peptide-1 receptor agonists (GLP-1 RA) has been used for glycaemic control and may reduce weight and the risk of cardiovascular disease in people with CKD.[21, 23] Iron has been recommended to address iron deficiency and anaemia in patients with CKD.[24, 25] Diuretics may be used to remove excess fluid and sodium and thus reduce blood

pressure and oedema.[26] Phosphate binders are also commonly used to manage hyperphosphatemia.[27]

Lifestyle management

Lifestyle management is also central to managing the risk of CKD progression and complications. In terms of diet, low sodium intake is typically recommended[28]. The Dietary Approaches to Stop Hypertension (DASH) is designed to be low in sodium, and involves the consumption of fruits, vegetables, whole grains, and low-fat dairy foods[29]. Salt substitutes can also improve the control of blood pressure, reduce all-cause mortality and cardiovascular events.[30] Low protein diets may help to slow the decline in kidney function.[31, 32] Some specific diets, such as the plant-based "Mediterranean-style" diet may also be recommended, which involves a reduction in the recommended dietary allowance values of protein, salt and phosphate intake for the general population (0.8 g/kg of protein, 6 g of salt and less than 800 mg of phosphate daily), and emphasises the intake of plant-based foods.[33] Limiting the consumption of acid-rich food and/or increasing the intake of alkaline-rich food may help to control metabolic acidosis. In some cases, dietary restriction of foods high in potassium may be recommended for patients with hyperkalaemia.[34, 35] Low-phosphorus diets may lower serum phosphate to reduce the long-term complications of CKD-mineral bone disorder.[36]

Over two thirds of adults with CKD do not meet the minimum recommended goal of physical activity (450–750 metabolic equivalents [METs]/min/wk),[38, 39] and lower physical activity and higher sedentary time are associated with frailty[40]. This situation worsens as kidney function declines, which leads to reduced functional capacity.[21] Guidelines recommend physical activity in patients with CKD and trials have demonstrated that meeting physical

activity guidelines can improve exercise capacity, cardiovascular fitness, cognitive function and quality of life.[30] Specifically, patients with CKD may be advised to undertake moderate-intensity physical activity for a cumulative duration of at least 150 minutes per week, or to a level compatible with their cardiovascular and physical tolerance.[3, 21] However, anaemia and loss of muscle might limit the functional capacity of some patients with CKD.[37]

Smoking cessation to reduce the risk of premature mortality from cardiovascular disease (CVD) in patients with CKD and may potentially help to slow the progression of disease.[46-49] The KDIGO guidelines for diabetes management in CKD recommend that patients with diabetic kidney disease who smoke should quit using tobacco products.[21] Smoking cessation aids such as nicotine replacement therapy, bupropion, and varenicline, as well has educational or behavioural-based programs may be considered.[50 51]

The management of CKD can be complex and burdensome for patients and may involve a trade-off between the potential benefits and risks of various interventions. Thus, evidence of such interventions based on outcomes of importance to patients, caregivers and clinicians is needed to support shared decision-making.

1.5 The need for a core outcome set in CKD

Informed decision-making remains limited because the outcomes of importance to patients with CKD who do not yet require kidney replacement therapy are not consistently reported in clinical trials. Fatigue, life participation, anxiety and depression are of priority to patients with CKD and their caregivers;[52] however, these are not frequently measured and in particular, patient-reported outcomes are often omitted from trials. Instead, surrogate biochemical

outcomes are more frequently reported in trials in CKD because of feasibility.[53] Systematic reviews have repeatedly shown that the outcomes reported in trials in haemodialysis, peritoneal dialysis and transplantation are extremely heterogeneous and are predominantly surrogate endpoints such as calcium, potassium and phosphate.[52, 54-56]

Across trials in patients with CKD who do not require dialysis or transplant, the outcomes reported in recent trials are also inconsistent with variability in the measures used. For example, kidney function has been reported across trials with different definitions and measures.[53] Three recent large trials in CKD (CKD-FIX [Controlled trial of slowing of Kidney Disease progression From the Inhibition of Xanthine oxidase], CREDENCE [Evaluation of the Effects of Canagliflozin on Renal and Cardiovascular Outcomes in Participants With Diabetic Nephropathy] and SONAR [Study Of Diabetic Nephropathy With Atrasentan] have reported and measured kidney function in different ways.[57-59]CKD-FIX measured kidney function as a single endpoint (change in eGFR) while CREDENCE and SONAR measured kidney function as a composite of end-stage kidney disease (dialysis, transplant or eGFR < 15 mL/min per 1·73 m2), doubling of serum creatinine and mortality. The time points for the definition of eGFR and duration of dialysis differed between CREDENCE and SONAR (30 days vs. 90 days). The variability in the outcomes and measures reported across trials in CKD and omission of patient-important outcomes makes it very difficult to compare the effect of interventions across trials and to make decisions based on outcomes that are meaningful to patients.

To improve consistency in reporting outcomes of critical importance to patients and health professionals across trials, the global Standardised Outcomes in Nephrology (SONG) initiative was launched in 2015 and has since established core outcome sets for trials in

haemodialysis,[60] kidney transplantation,[61] peritoneal dialysis,[62] polycystic kidney disease,[63] glomerular disease,[64] children and adolescents.[58] Core outcomes sets are an agreed upon standardised set of outcomes that should be measured and reported in all trials in a specific clinical field.[65] However, there is no core outcomes set for trials in CKD (CKD stage 1–5, not requiring kidney replacement therapy). The SONG-CKD initiative addresses a gap by establishing a core outcome set that will be co-produced by patients, caregivers, clinicians and researchers. This core outcome set is likely to help improve the relevance of trials for informed decision-making among patients with CKD and their caregivers and health professionals.

1.6 Aims of this research

The studies presented in this thesis collectively aims to establish a core outcomes set for patients with CKD not yet requiring kidney replacement therapy.

The specific aims of my thesis are:

1. To identify patient and caregiver priorities for outcomes in CKD (Chapter 2)
2. To describe the experiences of nephrologists on caring for patients receiving in-center hemodialysis during the COVID-19 pandemic in Latin America (Chapter 3)
3. To generate consensus among patients/caregivers and health professionals on critically important outcomes for trials in CKD prior to kidney failure and the need for kidney replacement therapy, and to describe the reasons for their choices (Chapters 4)
4. To establish a consensus-based set of core outcomes for trials in CKD (prior to the need for kidney replacement therapy) (Chapter 5)

5. To describe the perspectives of life participation in patients with CKD not requiring kidney replacement therapy in Latin America (Chapter 6)

1.7 Structure of the thesis

This chapter, Chapter 1, includes an overview of the literature on CKD, specifically the definition, classification and epidemiology of CKD, quality of life and symptoms in patients with CKD, management of CKD and the need for a core outcomes set for trials in patients with CKD not yet requiring kidney replacement therapy. The studies presented in this thesis are identical copies of published, peer-reviewed articles (Chapters 2, 3, 4, 5), and a submitted article (Chapter 6). The structure of this thesis is illustrated in Figure 1.1.

Chapter 2 describes the application of focus groups with nominal group technique as a mixed methods approach for generating consensus on patient/caregiver priorities for outcomes in CKD. Chapter 3 describes the perspectives of nephrologists on caring for patients receiving in-centre haemodialysis during the COVID-19 pandemic. As the COVID-19 pandemic occurred during my candidature, this caused a delay in the SONG-CKD project, and I pivoted my efforts to addressing the priority of COVID-19. Chapter 4 involves an international Delphi survey to generate consensus among patients, caregivers and health professional on outcomes of critical importance to be potentially included in the core outcomes set. Chapter 5 reports findings from a consensus workshop to establish the core outcomes for CKD. Chapter 6 describes the perspectives of patients, caregivers and health professionals on life participation (which was identified as a core outcome) in CKD not requiring kidney replacement therapy in Latin America. In Chapter 7, the final chapter of this thesis, the key findings from each study are combined and reflected upon as a cohesive whole. The strengths and limitations of the

studies are examined. The findings are compared with existing literature, and the implications for clinical practice, policy, and future research are discussed.

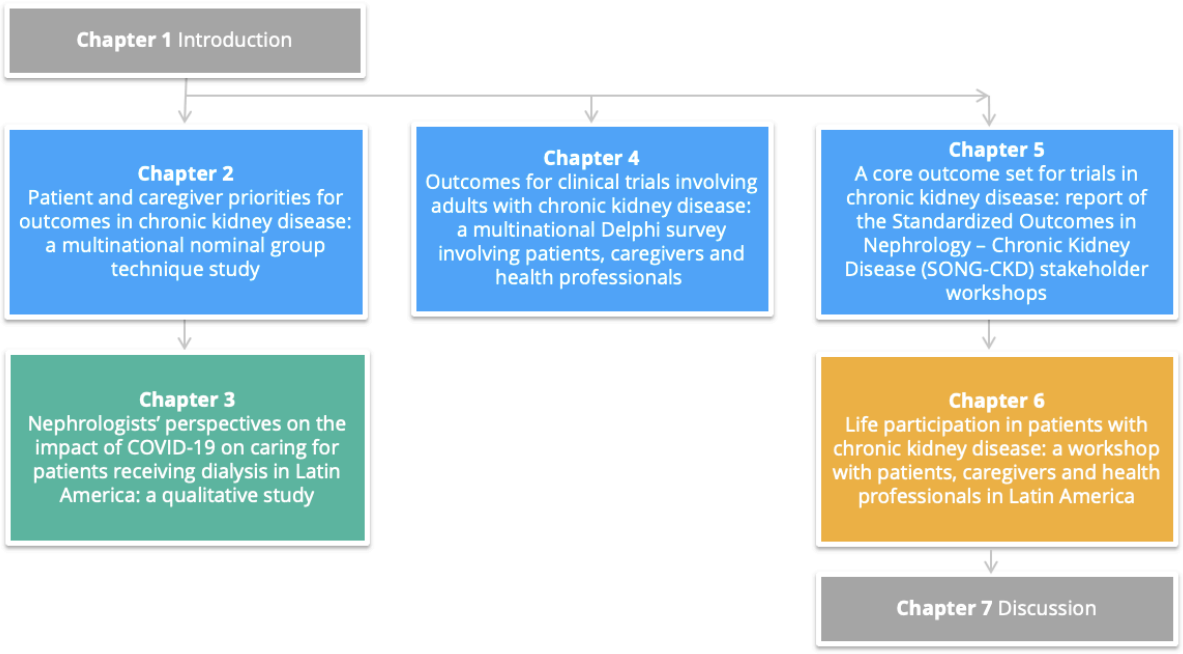

Figure 1.1 Thesis chapter outline

1.8 References

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Chapter 2: Patient and caregiver priorities for outcomes in chronic kidney disease: a multinational nominal group technique study

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This chapter is structured as per the journal article.

Chapter 2: Consensus methods – nominal group technique

2.1 Abstract

Rationale and objective: Patients with chronic kidney disease (CKD) are at an increased risk of premature death, cardiovascular disease, and burdensome symptoms that impair quality of life. We aimed to identify patient and caregiver priorities for outcomes in CKD.

Study Design: Focus groups with nominal group technique

Setting and Participants: Adult patients with CKD (all stages) and caregivers in the United States, Australia, and United Kingdom.

Methodology: Participants identified, ranked and discussed outcomes that were important during the stages of CKD prior to kidney replacement therapy.

Analytical Approach: For each outcome, we calculated a mean importance score (scale 0-1). Qualitative data were analyzed using thematic analysis.

Results: Sixty-seven (54 patients, 13 caregivers) participated in 10 groups and identified 36 outcomes. The five top ranked outcomes for patients were: kidney function (importance score = 0.42), "end-stage kidney disease" (ESKD) (0.29), fatigue (0.26), mortality (0.25) and life participation (0.20); and for caregivers the top five outcomes were: life participation (importance score = 0.38), kidney function (0.37), mortality (0.23), fatigue (0.21) and anxiety (0.20). Blood pressure, cognition and depression were consistently ranked in the top ten outcomes across role (patient/caregiver), country and treatment stage. Five themes were identified: re-evaluating and reframing life, intensified kidney consciousness, battling unrelenting and debilitating burdens, dreading upheaval and constraints, and taboo and unspoken concerns.

Limitations: Only English-speaking participants were included.

Conclusions: Patients and caregivers gave highest priority to kidney function, mortality, fatigue, life participation, anxiety and depression. Consistent reporting of these outcomes in

research may inform shared decision-making based on patient and caregiver priorities in CKD.

Conclusions: Patients and caregivers gave highest priority to kidney function, mortality, fatigue, life participation, anxiety and depression. Consistent reporting of these outcomes in research may inform shared decision-making based on patient and caregiver priorities in CKD.

2.2 Introduction

Globally, the prevalence of chronic kidney disease (CKD) ranges from 8 to 16%[1]. CKD is associated with an increased risk of mortality, cardiovascular events, hospitalization, and progression to kidney failure requiring kidney replacement therapy[2-6]. Cognitive impairment, depression, fatigue, and reduced physical function are also common in patients with CKD[1,7-11]. The management of CKD can be challenging because patients' symptoms and prognosis are highly variable and follow uncertain trajectories[12].

As such, there is recognition of the need for informed shared decision-making that explicitly considers the preferences and goals of patients[12,13]. This requires evidence on the impacts of disease and treatment that are important to patients. Prevention of progression of kidney disease, survival, and symptoms and side effects including fatigue, cramping, depression, pruritis, headaches, dizziness, and mood are some of the outcomes that have been identified as important by patients with CKD and their caregivers[14-18]. However, trials do not always

measure or report outcomes that are meaningful to patients[7,19]. In particular, patient-reported outcomes that reflect how patients feel and function are frequently omitted[20,21].

There is a need to ascertain a comprehensive and prioritized set of outcomes during the stages of CKD prior to the need for kidney replacement therapy, that are meaningful and relevant to patients and their caregivers. The aim of this study was to identify and prioritize outcomes important to patients and their caregivers for research in CKD, and to describe the reasons for their choices. This may inform the choice of outcomes for research to support shared decision-making in patients with CKD.

2.3 Methods

This study was conducted as part of a broader study on patient and caregiver perspective on nomenclature for kidney health and outcomes in CKD. This paper is specifically focused on the identification, prioritization and discussion of outcomes important for research in CKD. We included health outcomes including clinical, biochemical, and patient-reported (outcomes that reflect how patients feel and function[22,23]). We used the Consolidated Criteria for Reporting Qualitative Studies (COREQ) to report this study[24].

Participant selection

Chapter 2: Consensus methods – nominal group technique

Adult patients aged 18 years or over, with any stage of CKD (Stage 1-5 including those receiving dialysis (5D) and kidney transplant recipients (5T), and the caregivers (family member or support person involved in the patient's care), English-speaking, and able to provide informed consent, were eligible. Participants receiving kidney replacement therapy at the time of the study were included because they are able to reflect on relevant experiences prior to the need for dialysis or transplant. Participants were recruited from the Standardized Outcomes in Nephrology (SONG) Initiative Network using a standardized invitation email, and also by recruiting clinicians across four centers in the United States (Houston, Dallas), Australia (Sydney, Armidale), United Kingdom (London, Sheffield). Baylor College of Medicine, The University of Sydney, Imperial College Healthcare NHS Trust, and the University of Sheffield provided ethics/governance approval, and all participants provided written informed consent. We used a purposive sampling approach to ensure a diverse range of demographic (age, gender), and clinical (cause and stage of CKD) characteristics as was feasible. We provided participants a reimbursement of $50 USD (equivalent in local currency) to cover travel expenses. Adult patients 18 years or older with any stage of CKD (stages 1-5, including those receiving dialysis [5D] and kidney transplant recipients [5T]) and the caregivers (family member or support person involved in the patient's care), English speaking and able to provide informed consent, were eligible. Participants receiving kidney replacement therapy (KRT) at the time of the study were included because they are able to reflect on relevant experiences before the need for dialysis or transplant. Participants were recruited from the Standardized Outcomes in Nephrology (SONG)

Initiative Network using a standardized invitation e-mail and also by recruiting clinicians across 4 centers in the United States (Houston and Dallas), Australia (Sydney and Armidale), and United Kingdom (London and Sheffield).

Baylor College of Medicine, The University of Sydney, Imperial College Healthcare NHS Trust, and the University of Sheffield provided ethics/governance approval, and all participants provided written informed consent. We used a purposive sampling approach to ensure as diverse a range of demographic (age and sex) and clinical (cause and stage of CKD) characteristics as was feasible. We provided participants a reimbursement of US $50 (equivalent in local currency) to cover travel expenses.

Data Collection

We used the nominal group technique[25] embedded in focus groups to identify and rank outcomes important for research in CKD, and to discuss reasons for their choices. The nominal group technique is a structured method for group brain storming that encourages contribution from all group members, and facilitates consensus through prioritization and discussion of ideas[25,26]. The two-hour groups were convened in centrally located venues external to clinical settings from March to May 2019. We developed the question guide based on previous studies on identifying priority outcomes in patients on kidney replacement therapy[27-29]. (Supplementary Table 1) A single facilitator (AT, TG) moderated the group, and a co-facilitator (LD, JS, NSR, PLV, AB) recorded field notes. Participants were asked to: i) discuss their experiences and the impact of CKD and treatment prior to kidney replacement therapy; ii) identify outcomes they believed were important to assess in research; iii) to review a list of outcomes (initially 26 outcomes from selected systematic reviews of trials in CKD and to add additional outcomes as relevant (the facilitator also added outcomes identified from part i and ii of the discussion); see Supplementary Table 1); iv) rank the top

10 in order of importance; and v) discuss the reasons for their choices, focussing on the top three. We convened groups until data saturation, defined as when no new outcomes or concepts (reasons) were identified by subsequent groups. We audio-taped and transcribed all sessions.

Data Analysis

Nominal Group Ranking

The importance score for each outcome was computed as the average of the reciprocal rankings[29]. It incorporates the consistency of being nominated and the rankings given by the participants. The importance score (IS) for each outcome was computed as the average of the reciprocal rankings. The reciprocal ranking was defined as 1 over the ranking assigned by each participant to each outcome. For example, if mortality is ranked first by one participant and third by another, the reciprocal rankings will be 1 and 1/3, respectively. If the outcome was not ranked by the participant, it was given a 0 as the reciprocal ranking. A higher reciprocal ranking indicates higher priority of the outcome. This score takes into account the importance given to the outcome by the ranking and the consistency of being nominated by the participants. We used Stata/SE version 14.0 (StataCorp. College Station, TX) and the R version 3.2.3 (R Foundation for Statistical Computing, Vienna, Austria) to analyze the data.

Qualitative Analysis

We entered transcripts into HyperRESEARCH software (ResearchWare Inc. Version 3.7.3, Randolph, MA). Using thematic analysis with constant comparison, we inductively identified themes that reflected the reasons for the identification and prioritization of outcomes. Author A.M.G reviewed the transcripts line by line, assigned codes to meaningful segments of text, and compared the concepts within and across each focus/nominal group to develop preliminary themes. To ensure the themes captured the diversity depth of data, three investigators (AT, TG, PLV) read the transcripts and reviewed and discussed the themes with A.M.G until consensus was reached[30].

2.4 Results

Participant characteristics

Across the 10 focus groups, the 67 participants included 54 patients and 13 caregivers; 43 (64%) were female. We conducted three groups in the United States (n=21), four groups in Australia (n=28), and three groups in the United Kingdom (n=18). (Table 2, Supplementary Table 2). At the time of the study, 16 patients were not on kidney replacement therapy and 38 patients were on kidney replacement therapy (hemodialysis, n=14; peritoneal dialysis, n=4, kidney transplant n=20).

Nominal group ranking

In total, 36 unique outcomes were identified and prioritized. Overall, the top ten based on the importance score were: kidney function (importance score = 0.32), "end-stage kidney disease" ESKD (0.21), fatigue (0.20), mortality (0.19), life participation (0.19), blood pressure (0.14), cognition (0.10), and anxiety (0.08). (Figure 1). The top 10 for patients were kidney function (0.42), ESKD (0.29), fatigue (0.26), mortality (0.25), life participation (0.20), blood pressure (0.17), cognition (0.13), infection (0.10), pain (0.09), and cardiovascular disease (0.08). For caregivers, the top 10 were life participation (0.38), kidney function (0.37), mortality (0.23), fatigue (0.21), anxiety (0.20), depression (0.19), blood pressure (0.17), sleep (0.16), cognition (0.15), and ESKD (0.13). (Figure 1)

Both groups (patient not receiving and receiving kidney replacement therapy) ranked kidney function, mortality, fatigue, blood pressure, ESKD, cognition and life participation in the top seven. This was followed by pain, infection, anxiety among patients not on kidney replacement therapy; and infection, cardiovascular disease, and depression for patients receiving kidney replacement therapy. (Supplementary Table 3) Comparing by sex, the top five for women were kidney function (0.41), mortality (0.29), life participation (0.28), fatigue (0.24), and ESKD (0.21). The top five for men were kidney function (0.41), ESKD (0.34), fatigue (0.27), blood pressure (0.18), and mortality (0.17).

Across the three countries, seven outcomes were consistently among the top 10, kidney function, ESKD, mortality, fatigue, life participation, blood pressure and cognition. The top five ranked by participants in the United States were: ESKD (0.39), kidney function (0.31), mortality (0.24), fatigue (0.20), and life participation (0.18); in Australia were: kidney function (0.40), fatigue (0.31), life participation (0.30), mortality (0.21), and cognition (0.18); and in the UK were: kidney function (0.54), ESKD (0.13), mortality (0.31), blood pressure (0.24), and fatigue (0.24).

Themes

We identified five themes that explained participants' choices and prioritization of outcomes. The description of the themes in the following section applied to both patients and caregivers unless otherwise specified. Supporting quotations for each theme are provided in Table 2. A thematic schema to show the conceptual links among the themes and ranking of outcomes is provided in Figure 2.

Re-evaluating and reframing life

Despair in being confronted with death: Upon being diagnosed, some participants initially believed that CKD was terminal. They felt confronted by their mortality and risk of death, and thus gave higher importance to mortality – *"But when you're in early stage, you would want to know. That was the first question, am I going to die?'* Patients considered the

importance of outcomes based on their perceived associated risk with mortality. For example, they believed declining kidney function increased their risk of death. They worried about losing time with their *family – "Mortality. I have young children now. I started crying, my children are young."*

Making the most of life left: After the initial shock of receiving their diagnosis, some patients strived to make the most of the situation – *"Getting sick has made me appreciate things more, and I'm actually doing more with myself now. I'm more active, I'm more positive, and it took getting sick to do it so."* They gave higher priority to outcomes that enabled them to maintain their quality of life (e.g. life participation) and live as well as the could in the time they had left – *"I'm still living. I get out of bed, and I'm still living and still breathing. As long as I can do that, I'm going to carry on and be positive because life is short."*

<u>Intensified kidney consciousness</u>

Fear of needing dialysis: Participants feared the need for dialysis because it meant losing opportunities in life such as travelling. For this reason, some ranked kidney function, ESKD, anxiety and life participation highly – *"You're going to have to go do dialysis at some point…you watch the numbers go down. Can you think of a guillotine swinging? Getting lower and lower and lower and lower. (Anxiety)* Another patient stated, "*I watched dialysis*

break [my mum's] body down. I was determined not to be in that condition or those same issues once I went on dialysis."

Enabling self-management to prevent disease progression: Knowledge of their kidney function enabled them to monitor their kidney health and take action to manage their condition and slow its progression, and thus it was highly prioritized – *"I was told I would be on dialysis in three years. But if I did this and that and not that, I could stretch it out a bit. Well, it stretched out for 17 years."* Monitoring kidney function felt like a "waiting game."

Repercussions on cardiovascular health: Some participants were aware that blood pressure was associated with kidney disease, and that blood pressure and kidney disease increased their risk of cardiovascular events – *"The fluid buildup around your heart can put too much stress on your heart."* However, some participants assigned lower importance to these outcomes because they believe that could control the risk by taking medications.

<u>Battling unrelenting and debilitating burdens</u>

Impairing life activities and goals: The ongoing symptoms of kidney disease affected participants' abilities to do activities of daily living. Some experienced debilitating fatigue that prevented them from being able to do or finish simple daily tasks and lead a normal life – *"No matter how much sleep or rest or holiday, you still wake up feeling as tired as or tireder in the morning than you felt when you went to bed."* Some focussed on outcomes that were

threats to personal goals, for example, achieving parenthood – *"I didn't care about the kidney function, as long as they said I could still go ahead, and fall [become] pregnant."*

Mentally and emotionally incapacitated*:* Mental health and cognitive impairment were difficult to manage and interfered with daily living, including work – *"I asked my boss from our previous company to fire me because I made a mistake, I was like, how could I have done this? I must've just been absent mentally or just not been able to think about it when I was doing it. There were things that I was just like, I know this word, or I lose things."* Some expressed feeling depressed, grief, and in denial because of the diagnosis of CKD –*" It [CKD] is not happening now, not happening to me. My family used to call me the queen of denial! It is grief. Is it not?"* Some felt that these struggles were hidden – "*...you present yourself as healthy to the world. Yet, you really have all these struggling underneath it all,"* and not discussed in clinic – *"you don't tend to talk about your lack of cognition. You don't tend to talk about your depression, the feeling of isolation."*

<u>Dreading upheaval and constraints</u>

An uncertain and precarious trajectory: Some participants found it difficult to predict the course of their kidney disease, which was challenging to cope with. They felt their health was in constant danger and this contributed to and exacerbated their anxieties – *"This is a game where you do not get to know the rules until you start playing."*

Trauma of hospitalization: Participants who had been hospitalized described the pain, treatment and overall experience as frustrating and traumatizing, and some continued to feel distress after their discharge – *"I've really struggled with hospitals because I got stuck in the hospital for six months while they were trying to sort out a range of things. And it was just horrible."* Some felt disorientated and confused whilst in hospital as they did not feel completely aware of the situation – *"Any time I hear the word hospitalization, it's just like, okay, something serious is going on."*

Resigned to a bleak future: Some resigned themselves to the reality that their health could only deteriorate toward "end-stage of kidney disease" and realized they would eventually require kidney replacement therapy– "*It [my kidney] can never go back to its normal self. It's always going to be sick. Whereas your liver, it grows back or whatever but, the kidney, once you have this disease, there's no going back to 100%."*

Taboo and unspoken concerns

Enduring embarrassing issues: Some patients identified that certain outcomes were difficult to broach in the clinical setting, such as sexual function – *"intimacy suffers because kidney disease, that's the last thing you want to think about when you're feeling sick".* They felt doctors were reluctant to discuss such issues that were important to them – *"I was 23 and my husband was interested in sex. I'm anemic. So, it's like, okay, I'll just lay there honey, I'm sorry, you know? No, honestly, that is something that is not addressed."*

Problems unaddressed in time-limited consultation: Most participants felt frustrated that the questions about their health, in particular kidney function, were not discussed or explained adequately by clinicians – *"He just didn't explain anything to me, he thought that I didn't need to know what my kidney function is, he had it under control and that's all that mattered".* Some patients felt helpless – *"When you go see your specialist, here's your levels; here's your hat, you've had your 20 minutes."*

Vague implications of biochemical parameters: Some patients felt that they did not understand the biochemical parameters their doctors spoke about during their consultations. – *"The specialists walk in; they say a list of numbers, okay this number does that, that means you do this, that means you do that, goodbye."* They felt uncertain and lost without knowing the implications of these biochemical results on their physical and emotional health, symptoms, and prognosis – *"When you've just got a bunch of numerals there, you're like oh, okay. What does it refer to? What stage is it? What does that stage mean? It's not something any of us would just walk into an office and understand."*

2.5 Discussion

The outcomes of high priority to patients and caregivers for research in the stages of CKD prior to kidney replacement therapy were kidney function, life participation, mortality, fatigue, and ESKD. This was followed by blood pressure and outcomes related to mental

health including anxiety, cognition, and depression, which were prioritized higher compared with clinical outcomes of cardiovascular disease and hospitalization. This prioritization was underpinned by a number of reasons. The shock of the diagnosis and potential need for kidney replacement therapy prompted patients to re-evaluate their life and indicated mortality and life participation as high priorities so they could live as well as they could whilst they were still alive and prior to receiving dialysis. Some become focused on maintaining kidney health and slowing the progression of the disease (maintaining kidney function) and minimizing the risks of life-threatening comorbidities including cardiovascular disease. Some outcomes were highly prioritized because they disrupted daily living and threatened life goals, were overlooked by clinicians, or because they caused or exacerbated uncertainty, trauma, and distress.

There were some differences in the prioritization of outcome by patients and caregivers, CKD treatment stage, and by country. Based on the mean importance scores, caregivers gave higher priority to outcomes related to mental health and cognition. It is possible that the impact of depressive symptoms or anxiety in patients is apparent and also challenging for caregivers. Pain and anxiety were unique to the top 10 prioritized outcomes by patients not receiving kidney replacement therapy. This is perhaps expected as patients expressed strong anxieties about their diagnosis, progression of disease, and fear of dialysis. Of note, there appeared to be a predominant focus on death and dialysis in prioritizing outcomes, with relatively little reference to transplantation. This may be because some participants were not eligible for or could not access transplantation or had overriding fears about mortality and dialysis. It may also suggest the need for patient and caregiver education to emphasize transplantation as an option to minimize or avoid the need for dialysis.

Cardiovascular disease and depression appeared in the top 10 for patients who were on kidney replacement therapy. It may be that they had more time to become aware about the risks of comorbidities. Most of the top ranked outcomes were the same across the United States, Australia and United Kingdom (Supplementary Table 4). Cardiovascular disease and hospitalization were unique to the top 10 in the United States and ESKD was the top priority in the United States, compared with Australia and the United Kingdom where ESKD was ranked eight based on importance scores. A possible explanation is that universal health coverage is not provided in the United States and patients may be concerned about the financial consequences in accessing healthcare for these major medical outcomes. Anxiety and depression were in the top in Australia, perhaps because more caregivers were present. In the UK, pain and fluid/weight were in the top 10.

Other studies in the CKD population have also found that survival, slowing the progression of CKD, depression, cardiovascular disease, symptoms (fatigue, cramping, headaches, pruritis), and side-effects of medications are important to patients[14-18]. Having to adapt and cope with the uncertainty and unpredictability of the disease and the impact it also has on the family have also been noted in prior studies in CKD[31]. Comparison across treatment stage, the high priority given to the outcomes of mortality, life participation, fatigue, depression and anxiety, and cardiovascular disease are generally consistent with patient priorities identified in dialysis and kidney transplantation[27-29,32,33]. However, kidney function and cognition appear to be of higher priority in CKD. For patients, kidney function is an important indicator

of kidney health, prognosis – including the need to start dialysis, and to inform and motivate self-management.

Cognition was also important to patients in our study as it can interfere with work, can hamper functioning, and may not be addressed in clinical care. Cognitive impairment is common in patients with CKD[34]. Patients even in an early stage of CKD have an increased risk of cognitive impairment, specifically in the visual-spatial organization and memory (VSOM), scanning and tracking, and language domains[35]. Another study also found that lower eGFR is associated with worse global cognitive function and memory[36].

Our study involved a reasonably diverse sample of patients and caregivers from three countries. The mixed methods design using nominal group technique to identify and quantify the relative importance of outcomes, combined with focus group discussion to describe the reasons for their choices, generated comprehensive insights. However, there are some potential limitations. We took a broad approach to CKD and did not power the study for subgroup analyses, for example, by type or cause of CKD, or by stage of CKD. The participants were heterogenous group of patients with CKD, most of whom had kidney failure requiring kidney replacement therapy. However, participants were explicitly asked to identify and prioritize outcomes for CKD prior to the need for kidney replacement therapy. Participants were not asked to self-report their stage of CKD. Patients with early-stage CKD may not progress to kidney failure requiring kidney replacement therapy. We cannot determine if the importance of outcomes, for example ESKD, may different between patients with earlier stages of CKD compared with patients at a later stage of CKD. It is possible that

concerns may differ between patients with advanced CKD who received a kidney transplant and those patients with earlier stage CKD not requiring kidney replacement therapy, however this was not found in our study. Further work to assess the priorities of a larger population of patients at different stages of CKD may be able to determine differences in priorities by CKD stages. The transferability of the findings to low-income countries and non-English speaking populations is uncertain, as they were not included in our study. Finally, providing a pre-pared list of outcomes may have limited the discussion. Also, transplantation, including pre-emptive transplantation, was defined in our study as an intervention and was therefore not captured as an outcome in the context of this study. However, outcomes identified in the general discussion on the impacts of CKD and treatment were added to the list. Across the groups, 10 new outcomes were added.

Patient priorities for outcomes may not always be recognized by clinicians[37]. A recent study comparing patient and provider perception of priorities for older adults with advanced CKD found that providers were correct only 35% of the time[38]. We have identified patient priorities for outcomes in CKD, which can be explicitly addressed in patient education and shared decision-making to support patient-centered care. Of note, limited health literacy is recognized as a barrier to education in CKD[39]. Cognitive function has been found to explain associations between health literacy, physical health and depression[40]. Cognition, an important outcome for patients, needs to be explicitly considered and addressed in the context of patient education and care in CKD.

The prioritization of outcomes in this study will directly inform subsequent efforts through the Standardized Outcomes in Nephrology (SONG) initiative, to establish core outcomes for trials in CKD[41]. Consistent reporting of outcomes that are critically important to patients, caregivers and health professionals can strengthen trial-based evidence to inform decision-making.

For patients and caregivers, kidney function, life participation, mortality, fatigue and ESKD were outcomes of highest priority in CKD. Mental health, including depression, anxiety, cognition, and comorbidities such as cardiovascular disease, and debilitating symptoms were also of importance to patients. These priorities were driven by the shock and uncertainty of the diagnosis, avoiding the need for kidney replacement therapy, being able to do daily activities and achieve life goals, and the need to bring attention to concerns that often remained unspoken and unaddressed in clinical settings. There is a need to broaden the research agenda and care in CKD to improve patient-centered outcomes in this population.

Acknowledgements

We thank all the patients and family members who gave their time to participate in the study.

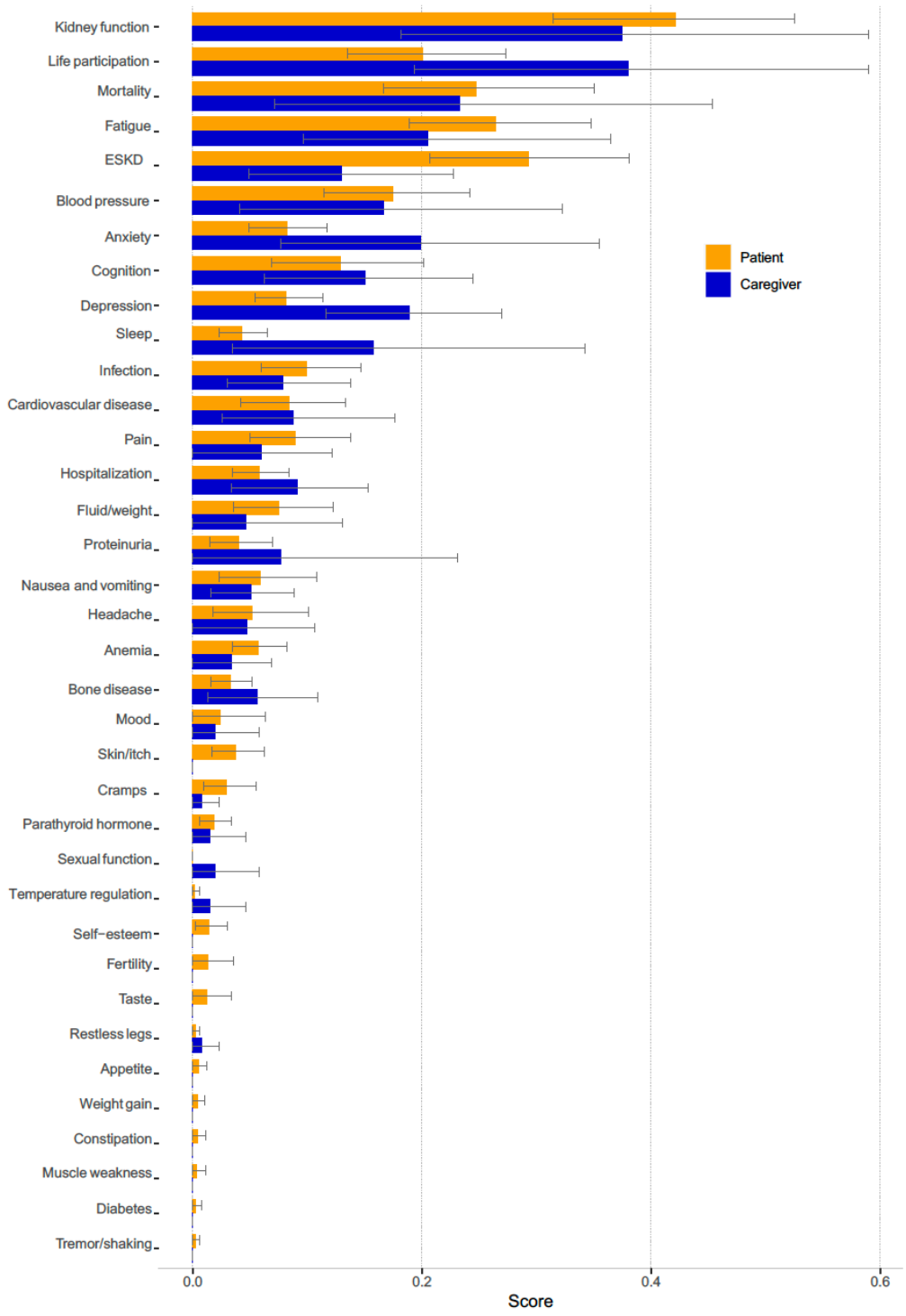

Figure 2.1 Importance scores for outcomes by patients and caregivers; ordered by the overall score. Shown are median scores, with standard error represented by error bars. Abbreviations: CVD, cardiovascular disease; ESKD, end-stage kidney disease; PTH, parathyroid hormone

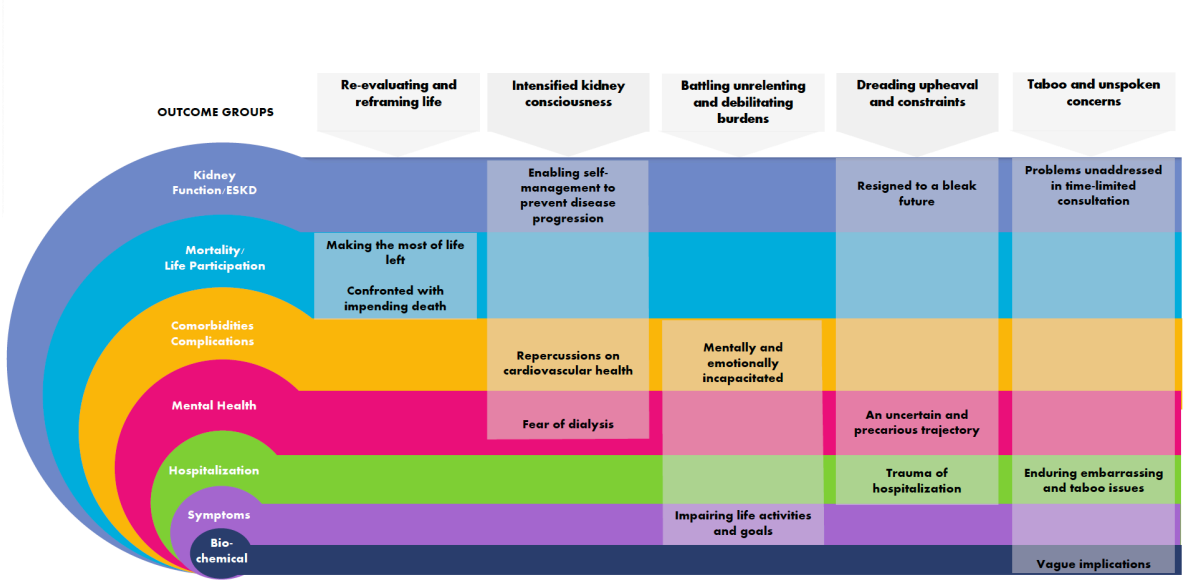

Figure 2.2 Schema depicting themes underpinning the prioritization of outcomes for chronic kidney disease by patients and caregiver. Abbreviation: ESKD, end-stage kidney disease

Table 2.1 Characteristics of participants (N=67)

Characteristics	n (%)
Role	
Patient	54 (81)
Caregiver	13 (19)
Sex	
Male	24 (36)
Female	43 (64)
Country	
United States (3 groups)	21 (31)
Australia (4 groups)	28 (42)
United Kingdom (3 groups)	18 ((27)
Ethnicity[a]	
White	46 (69)
African American	11 (16)
Asian	4 (6)
Other*	6 (9)
Age (years)	
18-30	4 (6)
31-40	8 (12)
41-50	12 (18)
51-60	23 (34)
61-70	15 (22)
>70	5 (8)
Marital status	
Single/widowed	18 (27)
Married/Partnered	39 (58)
Divorced/separated	10 (15)
Number of children	
0	18 (27)
1-2	32 (48)
3 or more	17 (25)
Employment	
Full time	24 (36)
Part time/casual	11 (16)
Student	3 (5)
Not employed/disability	13 (19)
Retired	16 (24)
Education	
Before 10th grade before 16 yrs	4 (6)
Completed 10th grade 16 yrs	5 (7)
Completed 12th grade 17/18 yrs	7 (11)
Professional certificate	11 (16)
Undergraduate degree	22 (33)
Postgraduate degree	18 (27)
Age at time of diagnosis*	
<18	5 (9)
18-30	11 (20)
31-40	10 (19)
41-50	13 (24)
>50	14 (26)

Cause of kidney disease*	
Diabetes	9 (17)
Hypertension	19 (35)
PKD	7 (13)
Glomerulonephritis	19 (35)
Infection	2 (4)
Immune/autoimmune	7 (13)
Reflux nephropathy	1 (2)
Unknown/don't know	3 (6)
Other[c]	6 (11)
Type of kidney replacement therapy (current)*	
None	16 (30)
Hemodialysis	14 (26)
Peritoneal dialysis	4 (7)
Kidney transplant	20 (37)
Duration of kidney replacement therapy (current)*	
Less than 12 months	4 (7)
1-3 years	13 (24)
4-6 years	7 (13)
More than 6 years	15 (28)

[a]Hispanic/Latino (n=1), Aboriginal Australian (n=1), Pakistani (n=2), Middle Eastern (n=1), Indian (n=1);
**Patients only (may include missing data if patients did not respond to the question)

Table 2.2 Illustrative quotes

Theme	Illustrative quotations
RE-EVALUATING AND REFRAMING LIFE	
Despair in being confronted with death	"And the first thing you think of is, dang, I'm going to die! You know? It's end stage. My kidney's going to stop working. I could wake up tomorrow and my kidney could be, you know? You could get hit with all that." (Female, US). "It's kind of a scary thing because when you have a kidney disease, you know that if your kidneys aren't functioning you're going to die. You just know that you're going to go to dialysis and you're going to die." (Female, UK) "But when you're in early stage, you would want to know. That was the first question, am I going to die?" (Female, UK).
Making the most of life left	"I want to live as long as I can, because I've got two grandchildren and three children and I want to see them for as long as I can. That's why I'm here." (Female, UK). "I'm not going to let this disease beat me. I am going to be on top of this. If it does, well I've done a lot of things in my life that I don't regret" (Female, Australia) "So, it doesn't actually really matter what the numbers say, and some of my numbers should have suggested that I should be feeling a lot worse than what I actually was, it's about how much I feel I can do and participate in my life and feel normal". (Female, Australia) "I'm really keen on living well. Looking at the future, my decisions of what will really help me to live well and to feel well, that will guide my decision-making at all stages of it". (Female, UK).
INTENSIFIED KIDNEY CONSCIOUSNESS	
Fear of needing kidney replacement therapy	"It's kind of a scary thing because when you have a kidney disease, you know that if your kidneys aren't functioning you're going to die. You just know that you're going to go to dialysis and you're going to die" (Female, UK) "Basically, when you hit level five [CKD Stage 5], it's time to either plan to meet your maker or go on dialysis. (Male, Australia)
Enabling self-management to prevent disease progression	"How much of the responsibility is ours in terms of, we have this disease whether we like it or not and we have to accept it. How much of that responsibility is to find out about it, to understand it, to educate ourselves, because it's my disease and I need to manage it because I'm the best person to do that, and how much of it should be the hospital's responsibility or physician's responsibility or GP's responsibility, at least to provide the right information? (Male, UK)
Repercussions on cardiovascular health	"For the kidney to be silent and long-term, but for blood pressure I feel it is more active and it can kill within no time." (Male, UK) "He [the patient] is all the time, saying, "Oh, it is my heart, it is my heart, it is my heart!"(Female, Australia)
BATTLING UNRELENTING AND DEBILITATING BURDENS	
Impairing life activities and goals	"I still want to be able to do what I've always done and I can't". (Female, Australia) "Fatigue was her number one thing. She was going to school full time, I don't know how she managed that. She'd go to school and come home and sleep the whole day." (Female, US) "I got frustrated because of the medications that they put you on. And I couldn't function on the court because it was messing with my vision and doing different things in my body that I'd never experienced before".(Female, US)

Mentally and emotionally incapacitated	"You have to realize that the other 35% of those toxins are still running around in your body. And they affect not only your, your organs, but they affect your brain, which affects your cognition, your emotions and all of that. I would find myself just snapping at my husband for just no reason at all. I mean, there are reasons I would just be, I wake up in the morning, just be irritated. I didn't want to be talked to, I didn't want to be bothered" (Female, US). "Just in terms of with any kind of disease and particularly since we're here discussing this there is a mental and emotional impact, finding out you have this, stages of grief and then there's things that you go through" (Female, Australia)

DREADING UPHEAVAL AND CONSTRAINTS	
An uncertain and precarious trajectory	"It's like knowing but not knowing, you sort of know what sort of track you're going down but you don't know what's on the way, or if you're going to stay on the way." (Female, UK)
Trauma of hospitalization	"When I go the hospital, my mom will come, and she'll immediately tell them, you better do something to sedate her, because she will, every 10 minutes, fight with you to leave here. If you want her to be here for any amount of time to help her, you need to give her something to calm her down, because after day one or two, I'll start demanding to leave" (Female, US).
Resigned to a bleak future	"I'll start. I'm first thing that comes to mind when I hear kidney disease is "no cure" (Female, US)
TABOO AND UNSPOKEN CONCERNS	
Enduring embarrassing issues	"You will go to your doctor and you will talk about your levels, you talk about your itchy skin. You don't talk about your sex drive". (Male, Australia)
Problems unaddressed in time-limited consultation	"Because the point is, from their perspective, what are they doing? They're monitoring us, they're managing us medically, they're worried about the GFR, they're worried about the medical aspect of the treatments" (Male, Australia) "When it started with me, there was only the specialist, and the GPs don't want to say too much. I would've liked to have been able to talk to someone…somebody that you can talk to about what is wrong with you" (Male, Australia) "I needed to know exactly where I was at with my kidney function" (Female, Australia)
Vague implications of biochemical parameters	"If they're talking to us about symptoms, they'd manage the symptoms and how we felt more than focusing on the numbers." (Female, Australia) "Because when they were talking to my family about the different stages, they said well, okay well stage two, stage two out of what? Three? Ten? What?" (Female, Australia)

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Chapter 3: Nephrologists' perspectives on the impact of COVID-19 on caring for patients undergoing dialysis in Latin America: a qualitative study

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This chapter is structured as per the journal article.

3.1 Abstract

Objectives: To describe the experiences of nephrologists on caring for patients receiving in-center hemodialysis during the COVID-19 pandemic in Latin America.

Design: Twenty-five semi-structured interviews were conducted by zoom videoconference in English and Spanish languages during 2020 until data saturation. Using thematic analysis, we conducted line-by-line coding to inductively identify themes.

Setting: 25 centers across 9 countries in Latin America.

Participants: Nephrologists (17 male, 8 female) were purposively sampled to include diverse demographic characteristics and clinical experience.

Results: We identified five themes: shock and immediate mobilization for preparedness (overwhelmed and distressed, expanding responsibilities to manage COVID-19 infection, united for workforce resilience); personal vulnerability (being infected with COVID-19, fear of transmitting COVID-19 to family); infrastructural susceptibility of dialysis units (lacking resources and facilities for quarantine, struggling to prevent cross-contamination, depletion of personal protective equipment and cleaning supplies); helplessness and moral distress (forced to ration life-sustaining equipment and care, concerned about delayed and shortened dialysis sessions, patient hesitancy to attend to dialysis sessions, grieved by socio-economic disparities, deterioration of patients with COVID-19, harms of isolation, inability to provide kidney replacement therapy) and fostering innovative delivery of care (expanding use of telehealth, increasing uptake of peritoneal dialysis, shifting focus on preventing syndemics).

Conclusions: Nephrologists felt personally and professionally vulnerable and reported feeling helpless and morally distressed because they doubted their capacity to provide safe care for

patients receiving dialysis. Better availability and mobilization of resources, and capacities to adapt models of care, including telehealth and home-based dialysis, are urgently needed.

3.2 Introduction

The SARS-CoV-2 related disease (COVID-19) pandemic has disrupted, delayed, and impeded access to treatment among individuals with chronic illness, including patients with kidney failure receiving maintenance dialysis[1]. For patients receiving long-term dialysis, their risk of acquiring COVID-19 is estimated to be five times higher, and they are four times more likely to die than the general population[2].

The pandemic has seen major reconfiguration of care in many health institutions to manage the increased demand to care for people with COVID-19. Unfortunately, this has inadvertently shifted resources away from the care of patients with other medical conditions, including kidney disease. Dialysis units have been faced with unprecedented challenges. For patients receiving in center hemodialysis (HD), physical distancing within the unit and during transportation can be difficult[3]. Clinicians caring for patients receiving dialysis have encountered a shortage of personal protective equipment (PPE) and could not access quarantine facilities for patients with infection[4]. Preventing infection in dialysis facilities is particularly challenging in resource-limited settings. For example, guidelines recommend against that the reuse of dialysis filters[5], however this remains to be common practice in some resource-limited settings, including in Latin America. Such regions, also contend with an increased risk of SARS-CoV-2[6] because of high-density housing and large socioeconomically disadvantaged communities.

However, little is known about nephrologists' experiences providing care to patients receiving dialysis; particularly in low-resource settings with high rates of COVID-19 infection, including Latin America. This study aims to describe nephrologists' perspectives on providing care to patients receiving dialysis during the COVID-19 pandemic to inform strategies for improving the quality and safety of care for patients receiving dialysis.

3.3 Methods

We used the Consolidated Criteria for Reporting Qualitative Health Research (COREQ)[7] (Supplementary File 1).

Patient and public involvement

Patients were not involved in this study as this study aimed to describe the perspectives of clinicians.

Participant selection

Nephrologists caring for adults receiving dialysis, including hemodialysis and peritoneal dialysis, in Latin America, irrespective of years of clinical experience in dialysis settings, were eligible to participate. We used purposive sampling to include participants across a diverse range of ages, gender, years of clinical experience, and countries. Nephrologists were identified through our professional networks (SLANH- Sociedad latinoamericana de nefrología e hipertensión) and

invited by email to participate. Participants could nominate other colleagues to participate. All the participants were given a consent form to participate. This study was approved by the Ethics Committee of the University of Sydney (2019-899).

Data collection

The interview guide was developed based on the literature and discussion among the investigators (Supplementary File 2). Two authors (A.M.G, A.H) conducted semi-structured interviews in English or Spanish language (as preferred by the participant) by zoom videoconference from June 2020 to November 2020 until data saturation. Author A.M.G, a PhD candidate with experience in qualitative studies, had practiced as a dietitian, in dialysis units in Chile. Her interest in the impact of COVID-19 and knowledge of the health system informed to the conceptualization of the research, design, data collection and analysis. The interviews were recorded and transcribed in English and Spanish.

Data analysis

Using inductive thematic analysis and drawing from the principles of grounded theory, author A.M.G performed line-by-line coding of the transcripts, used constant comparison within and across transcripts, and inductively identified preliminary concepts. Similar concepts were grouped into themes and subthemes, and patterns were identified among themes. The interview transcripts were imported into HyperRESEARCH (version 4.0.1 ResearchWare Inc. Randolph MA). Investigators A.H., E.L., S.C., A.J., reviewed the themes to ensure that the analysis

captured the full range and depth of the data obtained. We conducted a member checking whereby the preliminary findings were sent to participants for comment and integrated any additional insights into the final analysis.

3.4 Results

Participant characteristics

All 25 invited nephrologists (100% response rate) participated, from 25 centers across 9 countries (Chile, Colombia, Uruguay, Guatemala, Peru, Bolivia, Brazil, Argentina, Mexico) (Table 1). Of the participants, 8 (55%) were women; 17 (59%) were from countries where English was not an official language, and 9 (18%) were from low- and middle-income countries. The average duration of the interviews was 35 minutes (ranging from 30 to 42 minutes). Nine participants responded to the preliminary findings and confirmed that the findings captured their perspectives.

Themes

We identified five themes: shock and immediate mobilization for preparation, personal vulnerability, infrastructure susceptibility of the dialysis unit, helplessness, and moral anguish, promotion of innovative provision of care. The respective subthemes are described below with illustrative quotations provided in Table 2.

Shock and immediate mobilization for preparedness

Overwhelmed and distressed: Participants were overwhelmed and unprepared for the sudden and severe consequences of COVID-19 and were distressed by the high mortality rates in patients receiving dialysis. They faced “chaos” and a “tsunami of demands” in making rapid changes to minimize the risks of infection in the dialysis setting, and to accommodate an unexpected increased “demand” in the number of patients requiring acute dialysis. It was stressful and exhausting having to constantly remain “alert” in facing such a medical emergency.

Expanding responsibilities to manage COVID 19 infection: Some took on additional responsibilities and cared for non-dialysis patients with COVID-19 and thus felt pressure to high-level skills for treatment they were less familiar with, for example, oxygen therapy and mechanical ventilation – “In hospitals, they throw you to the wolves without you knowing how to provide oxygen; they tell you: just do it.” For some, having to administer treatments for managing COVID-19 was “new” and challenged their “comfort zone.”

United for workforce resilience: Dialysis centers faced a critical shortage of staff; some nephrologists were unable to work because their older age placed them at increased risk for worse outcomes if infected with COVID-19 and other nephrologists were unavailable because they strived to work on “the front line”. Younger participants were committed to help because they believed they had a lower risk of developing severe disease. Confronting the pandemic together cultivated team solidarity, and they were conscious of supporting each other – “Every day we would discuss, talk, and approach the health staff, with questions like how you are doing, how are you, or what you need?". Some chose to prioritize their clinical responsibility to patients

over their own personal commitments - "I put aside crucial personal things temporarily because this is my job."

Personal vulnerability

Being infected with COVID-19: Participants were terrified about their own risk of being infected with COVID-19 and tried to stay healthy and said they were "fighting and resisting" the virus. They stated, "it was very uncertain, we are waiting to get sick, we don't want to expose ourselves."

Fear of transmitting COVID-19 to their family: Some were worried about bringing the virus home and infecting family members. That was their "primary concern" because they could not predict if their family would be exposed to severe illness and even death from COVID-19. Some noted their colleagues suspended clinic work because they had vulnerable family members, or those who continued to work chose to isolate themselves from their family – "I sent my family away from Santiago these five months, because it was very intense."

Infrastructural susceptibility of the dialysis unit

Lacking resources and facilities for quarantine: Participants despaired for patients who had COVID-19 as there were insufficient quarantine facilities in the dialysis unit to meet the demand. They could not isolate patients with COVID-19 from their family members. In some countries,

participants felt helpless as dialysis units were “running out of space and collapsed.” Participants were devastated as their patients could not access dialysis and died at home.

Struggling to prevent cross-contamination: At the onset of the pandemic, participants turned much of their attention and resources to preventing exposure to COVID-19. It was challenging to enforce social distancing, avoid “crowds in the waiting room,” and for staff and patients to wear personal protective equipment. Participants noted that patients took their masks off in the vehicle in which they were transported to and from the dialysis unit – “if one patient becomes infected, he or she will infect the entire van because they spend more than an hour and a half or two hours being transported by the van in a closed space". In some countries, reusing dialysis filters were no longer permitted– “here we reuse the dialysis filters. That procedure had to be suspended also when patients had coronavirus.”

Depletion of personal protective equipment and cleaning supplies: Some faced an insufficient supply of personal protective equipment for patients and clinicians – “you cannot give everything to everyone because there is a lack of resources.” It was stressful to ration supplies between patients and clinicians – “we wanted to put masks on our patients but initially our hospital did not give us permission to do so because they were very afraid that they did not have enough supplies for everyone.”

Helplessness and moral distress

Forced to ration life-sustaining equipment and care: Some had to make harrowing decisions about rationing life-sustaining treatments, in particular dialysis and mechanical ventilation. One participant explained, “I would have made the effort to offer dialysis to two critically ill patients with COVID, but I gave up on offering dialysis. They had no chance of receiving dialysis because there was no dialysis machine.” They were also forced to allocate ventilation to patients receiving dialysis in the hospital setting, who they judged to have a better prognosis. They had to do “war medicine” and “tried to distribute the few resources that were available as best as they could.” Some felt judged by others and the dire consequences on patients caused anguish and guilt – "The tremendous challenge of playing God, in the sense of who lives and who does not live, who has the right to be connected or not."

Concerned about delayed and shortened dialysis sessions: Participants were concerned about having to reduce the dialysis prescription for patients to account for the increased time taken to implement strict cleaning protocols due to COVID-19, also to ensure that other patients could receive dialysis – “I had six patients who had to dialyze, and you had only one machine, and there you had to cut dialysis time.” Dialysis units were understaffed because staff members had contracted COVID-19 or were unable to work – “I have less staff to dialyze people, and I have to dialyze shorter.” Some tried to refer patients to private dialysis units, but those units could not accommodate additional patients.

Patient hesitancy to attend dialysis sessions: Participants explained about some hesitancy by patients to attend in-center dialysis because of fear of being infected with COVID-19, which caused worry, helplessness, and frustration – “This morning, the largest public hospital adapted

an area to dialyze COVID-positive patients on a fourth shift. Therefore, this morning patients went on a hunger strike at the entrance door. They were not letting patients enter because they said they were going to infect them." They stated that patients were afraid of the possibility of dialyzing near patients with COVID-19.

Grieved by socio-economic disparities: Participants were saddened that, patients from low socio-economic backgrounds were more disadvantaged because of COVID-19 – "many patients are do not work and receive miserable pensions. They cannot leave their home and they face difficulties accessing food." They explained that "where the poorest patients are dialyzed, it is shocking to see how patients arrive at the emergency room and cannot access a hospital bed, and many of them end up dying."

Deterioration of patients with COVID-19: Some participants did not expect COVID-19 would have severe and ongoing symptoms and complications and observed how dialysis patients were in a severely weakened state after being infected, "with much sarcopenia that caught my attention". However, participants commented that "rehabilitation is what we least think about now because we have to prepare for the waves that come next."

Harms of isolation: Due to the COVID-19 protocols, the dialysis sessions were described as "a bit depersonalized". Health professionals had to wear a mask and glasses and participants mentioned that patients "had no idea with whom they were talking to". Participants sought to provide emotional support because the "patients were very alone"; and for patients with COVID-19, "there were no visits at any time, and every day for them was the same of others". They

noticed that patients were "quite depressed" and that some patients, "knew they were going to die".

Inability to provide transplantation therapy: In some countries, participants explained that their kidney transplantation programs were suspended during the COVID-19 pandemic. Participants reported they did not have beds for transplantation because "they were all used by COVID patients" and "there is a long list of dialysis patients waiting for a transplant". Likewise, patients with kidney transplantation who come to be monitored with some frequency stopped attending hospitals or clinics. They noticed that patients stopped their following up – "COVID-19 devoured them". Participants highlighted having no idea about where their transplant patients, how they are doing or if they have controlled their immune response – "I have a considerable fear of what will happen to them".

Fostering innovative delivery of care

Expanding the use of telehealth: Participants remarked that telehealth "had to be implemented rapidly" because of the pandemic. Participants described how telehealth "has allowed us to continue working remotely in hemodialysis's units. This is good because we can conduct nephrology consults during the COVID-19 pandemic". Telemedicine provided them a safe, effective, and efficient way of communication – "patients send us messages when something happens, and don't have to travel more than 800 kilometers to see the doctor".

Increasing uptake of Peritoneal dialysis (PD): Some participants expected that there would be an increase in the number of patients who choose peritoneal dialysis over hemodialysis during the pandemic – "We see less complications with peritoneal dialysis than with hemodialysis ". They recognized that for patients receiving PD "the risk is minimal" and could be managed through telemedicine.

Shifting focus on preventing syndemics: Participants explained that patients with comorbidities were at an increased risk of severe infection – "patients with chronic disease, including those with kidney disease, suffer the most when developing complications from COVID-19 infection", and that these clustered within socially disadvantaged and vulnerable groups, and thus had concerns about inequity. They stated that, "a relatively large number of dialysis patients have died in the world, particularly in our Latino communities". They urged for a focus on addressing the "syndemic"; "this world is treating the pandemic's symptoms, and they are not looking for the causes of this as a syndemic"; and called for a more comprehensive approach, encompassing education, employment, housing, food, and the environment – "a comprehensive vision is needed if we are to protect the health of our communities."

3.5 Discussion

Nephrologists caring for patients receiving in-centre HD in Latin America during the COVID-19 pandemic felt overwhelmed. They had to suddenly mobilize resources to prevent the dialysis patients' and others' exposure to COVID-19 and simultaneously manage individuals who were COVID-19 positive. A major challenge was contending with the susceptibility of dialysis units

to cross-infection, particularly with the lack of resources for quarantine and PPE supplies. They felt personally vulnerable in being exposed to COVID-19 infection, and the flow on risks to their own families. Having to ration life-sustaining treatment and being unable to provide adequate dialysis and witnessing the trauma of patients being isolated compounded a sense of helplessness and moral distress among nephrologists. The challenges provided an impetus for nephrologists to change the delivery of care with a focus on increasing the use of telehealth, home-based modalities, and preventing syndemics.

The findings were broadly consistent across participants. Nephrologists were concerned about the susceptibility of dialysis units including the lack of PPE, resources for quarantine, and cross-contamination. There appeared to be some differences in the availability of resources at the clinic in which they worked, which was determined by the resources, and the roles in which they had to take on. Due to the risk of infection, some participants reported suspending some procedures such as the reuse of filters, a common practice in dialysis centres in Latin America. They felt helpless about the socioeconomic disparities as patients in low resource areas faced substantial barriers to accessing healthcare and had worse outcomes.

Whilst there are very few studies on nephrologists' perspectives on the care of patients receiving dialysis during the COVID-19 pandemic, similar challenges have been identified across other medical disciplines. Clinicians have described the angst of having to ration[8] and withhold treatment and experienced tremendous physical and psychological burden. In studies conducted across China, the USA, and Europe, clinicians have reported increased anxiety, depression, and symptoms of post-traumatic stress disorder[9]. Studies in the United States have also identified that

Latinx communities are severely disadvantaged in terms of accessing healthcare, and patients were afraid of unemployment, eviction, and inability to protect themselves from COVID-19 as they lived in high-density housing[10]. However, specific to the context of dialysis, nephrologists were particularly concerned about patients receiving inadequate dialysis due to the shortened sessions, patient hesitancy to attend dialysis, preventing infection in dialysis units, and suspension of transplantation programs, further increasing the waiting lists in some Latin American countries.

Compared with the perspectives of clinicians, patients receiving dialysis and caregivers have also reported feeling distressed and vulnerable in dialysis settings during the COVID-19 pandemic, particularly if they observed inadequacies and inconsistencies in infection control practices[11]. Patients receiving dialysis reported that they were concerned about the cancellation of follow up appointments as they could not monitor their blood results, missed dialysis sessions, and were anxious about risk of complications such as hyperkalaemia[12, 13]. However, patients have emphasized concerns about the potential loss of or delay in receiving a kidney transplant[14].

Our study generated comprehensive insights about nephrologists' perspectives on caring for patients receiving dialysis during the COVID-19 pandemic. We conducted interviews until data saturation and used member checking and investigator triangulation to ensure that the findings captured the data collected. However, there are some potential limitations. The participants did not mention the impact on caregivers. Some findings suggest that family caregivers of patients undergoing in-centre HD should be considered by the dialysis team to develop educational and supportive interventions to meet family caregivers' needs, mitigate emotional distress, fears, and

concerns, and prevent caregiver burden during the COVID-19 pandemic[15]. All participants were from Latin America, and thus the transferability of the findings beyond this region is uncertain.

The prevention of "syndemics," defined as a synergistic interaction between multiple epidemics or disease clusters (i.e. SARS-CoV-2 infection and non-communicable diseases)[16,17] that exacerbate worse health outcomes, was also identified as a priority. Nephrologists recognized that the impact of the pandemic on patients with CKD and receiving dialysis was intensified because of its diverse nexus of intertwined biological (including comorbidities) and socioecological factors. Therefore, they advocated the need for the health system not to have a single-disease focus but to ensure comprehensive whole-person care. It has been argued that the COVID-19 pandemic has escalated into a syndemic due to several driving factors: overcrowding, loneliness, uncertainty, poor nutrition, and lack of access to health services; and consequently, depression, suicide, domestic violence, and psychiatric illnesses have significantly increased[17]. Social determinants of health, such as poverty, social inequality, social stigma, and the environment where people live and work, significantly affect the intensity of the syndemic[18].; which is apparent in the dialysis population particularly in resource-poor settings.

3.6 Conclusion

Nephrologists felt vulnerable, helpless, and moral anguish because they were unable to provide access to quality and safe care for patients receiving dialysis. In particular, they were concerned that patients were not receiving an adequate prescription of dialysis with many patients also refusing to attend dialysis sessions. They struggled with infection control measures due to the

lack of resources for quarantine and PPE. They also encountered anguish and guilt from having to ration treatment. Better availability and mobilization of resources, and capacities to adapt models of care (i.e. telehealth, home-based dialysis) are urgently needed. This may also help to prepare for future pandemics beyond COVID-19, to minimizes the consequences on the care and outcomes of patients receiving dialysis.

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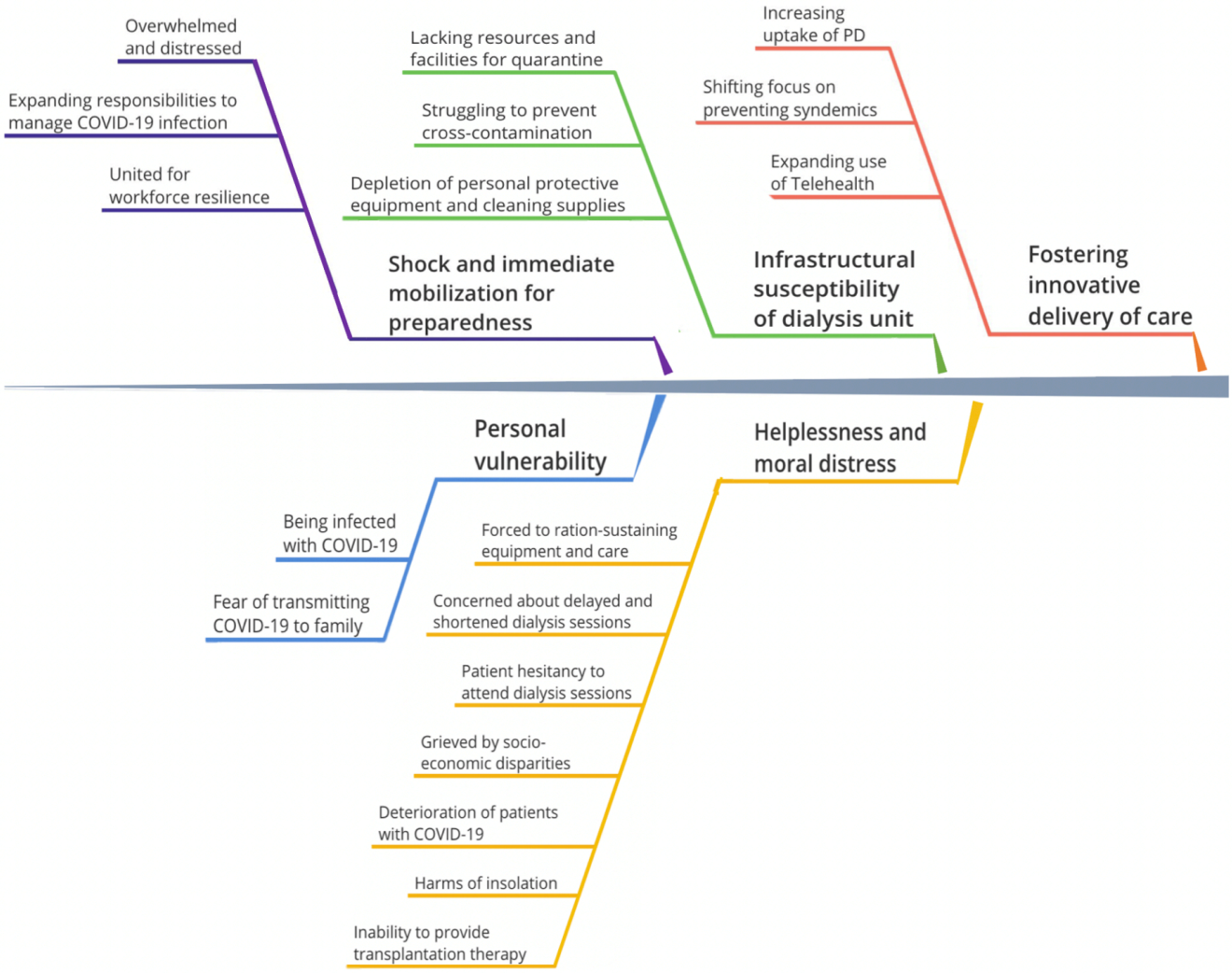

Figure 3.1 Thematic schema: The five themes from the study were shock and immediate mobilization for preparedness (overwhelmed and distressed, expanding responsibilities to manage COVID-19 infection, united for workforce resilience); personal vulnerability (being infected with COVID-19, fear of transmitting COVID-19 to family); infrastructural susceptibility of dialysis units (lacking resources and facilities for quarantine, struggling to prevent cross-contamination, depletion of personal protective equipment and cleaning supplies); helplessness and moral distress (forced to ration life-sustaining equipment and care, concerned about delayed and shortened dialysis sessions, patient hesitancy to attend to dialysis sessions, grieved by socio-economic disparities, deterioration of patients with COVID-19, harms of isolation, inability to provide kidney replacement therapy) and fostering innovative delivery of care (expanding use of telehealth, increasing uptake of peritoneal dialysis, shifting focus on preventing syndemics).

Table 3.1 Participant characteristics (N=25)

Characteristic	N	%
Sex		
Female	8	32
Male	17	68
Age group (years)		
30-39	1	4
40-49	8	32
50-59	10	40
60 and over	6	24
Center volume (number of patients receiving dialysis)		
1-20	3	12
21-40	1	4
41-60	2	8
More than 60	19	76
Dialysis setting*		
Outpatient dialysis units	14	56
Hospital	16	64
Care for patients with confirmed COVID-19		
Yes	21	84
No	4	16
Tested for COVID-19		
Yes	12	48
No	13	52
COVID-19 test result		
Positive	1	4
Negative	24	96
Country*		
Chile	13	52
Colombia	3	12
Uruguay	2	8
Guatemala	2	8
Peru	1	4
Bolivia	1	4
Brazil	1	4
Argentina	1	4
Mexico	1	4

*Percentage may not equal to 100% as participants could have experience in multiple settings

Table 3.2 Selected illustrative quotations to support each theme

Theme	Quotations
Shock and immediate mobilization for preparedness	
Overwhelmed and distressed	*"We become in little machines to make decisions, with a high emotional cost" (Male 40-49 age group, Chile).* *"200 dead in one day, dam! there is a stab in the back. The distress of colleagues and the health professionals is enormous" (Male 60-69 age group, Chile).* *"It is shocking to see all the mortality. It has been painful for our patients and us. Every week they inform us: [patient A, B, C] did not survive and died" (Female 50-59 age group, Chile).*
Expanding responsibilities to manage COVID 19 infection	*"We went as a team, gaining experience, but at first, it was like a hit in my head. We did not know what we were up against" (Female 50-59 age group, Chile).* *"I have had to learn a lot about COVID, about acute kidney failure, about mechanical ventilation, because of this emergency" (Male 40-49 age group, Chile).* *"So, we have to adapt, study and collect others' experiences since nothing was known about this virus. Everything has been new" (Female 30-39 age group, Chile).*
United for workforce resilience	*"Everything has changed in my life. I was focused on being well to collaborate and being useful in the pandemic, putting aside personal projects because this is my vocation. I could not subtract myself, there was a spirit to serve, help, and resist" (Female 30-39 age group, Chile).* *"We had a very nice movement, lovely behaviour of the health workers, students. They proactively asked to help because they are young, and low risk" (Male 47-49 age group, Brazil)* *"During this COVID period, we have learned to work as a team, everyone giving his best" (Male 40-43 age group Chile).*
Personal vulnerability	
Being infected with COVID-19	*"It was very uncertain, waiting to get sick, exposing oneself, or hiding. I was scared" (Male 40-49 age group, Chile).* *"How to combat the fear of getting ill, first as a human being, and then as a member of a health team. How to prevent the infection from your patients, and it does not affect you" (Male 60-69 age group, Chile).* *When the patients got infected, I checked their symptoms when I got home. "This hurts me, it hurts there" (Female 60-60 age group, Chile).*
Fear of transmitting COVID-19 to family	*"I am most concerned about spreading the virus to my family rather than getting sick myself." (Female 50-59 age group, Chile)* *"Old and young people have died, and you can be responsible for infecting your family members by bringing the virus home." (Male 50-59 age group, Colombia)* *"Health personnel with risk factors, or who fear infecting their family members, were absent"(Female 30-39 age group, Chile).*
Infrastructural susceptibility of dialysis unit	
Lacking resources and facilities for quarantine	*"Having no control during the pandemic has made it impossible for patients to access medicine. We are running out of space in the units because they have not been followed up on, have stage 5 and need dialysis urgently." (Male 40-49 age group, Bolivia).* *"Patients cannot eat anymore during the dialysis session, we have had to adapt the dialysis centres 24x7 with separations, so they have the minor contact possible." (Male 40-49 age group, Chile).* *"The dialysis access has been cut off. "We are trying to make our stage five patients endure as long as possible, medically and nutritionally, to prevent complications." (Female 50-59 age group, Chile).*
Struggling to prevent cross-contamination	*"Dialysis patients do not have a quarantine; it is an armchair and a different shift than usual." (Female 50-59 age group, Chile).* *"some patients must take public transportation to go home.. This is exactly the opposite of what we are trying to prevent cross-contamination in the units, to take care of them." (Male 40-49 age group, Brazil).* *"Some patients have bought biosecurity suits and wear them while walking in the street or while putting on gloves without washing their hands." (Male 40-49 age group, Bolivia).*
Depletion of PPT and cleaning supplies	*"We wore shoe covers that, after a short time, were no longer available due to a lack of resources. So you place quaternary ammonium rubbers on the floor to clean feet" (Male 60-69 age group, Chile).*

	“As opposed to using alcohol on hands, they put a hand wash at the entrance. "We were doing it due to lack of supplies, to protect them and ourselves.” (Female, 40-49 age group, Chile). *“Our protections were not sufficient, so it was very scary." (Female, 30-39 age group, Chile).*
Helplessness and moral distress	
Forced to ration life-sustaining equipment and care	*"The most severe problem is access to respirator treatment. There have been many such cases, and we have seen many deaths at home" (Male, 50-59 age group, Chile).* *"They do not seem to take the patients into account much. They treat them like high-risk patients without recovery and don't put them on a ventilator." (Female, 60-69 group of age, Chile).* *"I understood that the patient died from a lack of dialysis, not from severe organ failure. However, the patient died because of the lack of access to dialysis" (Male, 40-49 age group, Chile).*
Concerned about delayed and shortened dialysis sessions	*“Patients did not receive an accurate dialysis because of all covid protocol measures you have to take." (Female, 50-59 age group, Chile).* *“We reduced dialysis time because the hospitals and private units were overstretched. So dialysis is sometimes started late, or the dose is not adequate”. (Male, 40-49 age group, Chile).* *"We do not provide the best quality dialysis because we have less staff to dialyze people, and I have to dialyze people shorter" (Male, 40-49 age group, Chile).*
Patient refusal to attend dialysis sessions	*"Some patients are afraid of going to the hospital. Other patients take medications on their own, to avoid going to the institution." (Male, 50-59 age group, Peru).* *“Due to COVID, a patient decided to come only twice a week. A revolver cannot be held to his head to make him attend all three sessions." (Female, 60-69 age group, Uruguay).* *“A fourth shift of dialyzing COVID-positive patients was started this morning at the largest public hospital. Therefore, patients staged a hunger strike at the entrance door. They were refusing to let patients in because they believed they would infect them."(Male, 40-49 age group, Bolivia)*
Grieved by socio-economic disparities	*"It is very difficult to realize that people who undergo dialysis are really sick and have no other alternatives." (Male, 40-49 age group, Chile).* *"Many patients do not work and receive miserable pensions. They are also unable to go out and cannot afford food.” (Male, 60-69 age group, Chile).* *“The lack of access to hospital beds in sectors where the poorest are dialyzed is quite shocking. Consequently, many of them die." (Male, 40-49 age group, Chile).*
Deterioration of patients with COVID-19	*“We have seen that people, both the staff and patients with positive covid, are very physically impaired.” (Male, 60-69 age group, Chile).* *“After the worst moment, we were left with many chronic patients, and what we deeply owed was rehabilitation. Sadly, these patients were wasted after spending two, three, or four weeks in the intensive care unit (ICU). “ (Male, 40-49 age group Chile).* *The medical community does not give much thought to rehabilitation. With the second wave, we must prepare for what is coming next, so we have little vision for the future." (Male, 40-49 age group, Chile).*
Harms of isolation	*"Patients and professionals had to wear masks and glasses, so the patient didn't know who he was talking to. No one visited them at any time, and every day was the same for them. They felt very alone." (Male, 40-49 age group, Chile).* *“There is much fear and uncertainty in the patients' faces about what is going to happen. Some of them are delivered to death, and they know they are going to die. Because some wanted to be accompanied, share with families, or talk, it was distressing." (Male, 40-49 age group, Chile).* *“Many doctors bring in screens to help patients communicate, but the most important thing is that you arrive at the emergency room without knowing if you have covid positive relatives until a week or ten days later. The isolation is horrifying." (Female, 50-59 age group, Chile).*
Inability to provide kidney replacement therapy	*“As a precaution, the living donor transplant was halted. The cadaver donor transplant was also stopped shortly after. By the time we realized we could resolve the issue, we no longer had beds because all of them were being used by COVID patients” (Male, 40-49 age group, Chile).* *“Some transplant patients were infected with COVID, and one of them died. Thus, when someone appears to have a fever, we call them, monitor them, and hospitalize them if needed." (Male, 40-49 age group, Chile).* *“CKD patients disappeared overnight. COVID ate them up. One does not know where they are, how they are. I am frightened of what will happen to them." (Male, 40-49 age group, Chile).*
Fostering innovative delivery of care	
Expanding use of telehealth	*Getting used to the fact that no by person consultation is required, getting used to telehealth” (Male, 40-49 age group, Bolivia).*

	“We have a chat group where our patients ask questions, and if something happens, I send a message and come right away." (Female, 60-69 age group, Uruguay). *“The prescription was sent to them via message, and they stay at home, sheltered, and come to the hospital as little as possible." (Male, 40-49 age group, Chile).*
Increasing uptake of PD	*"COVID patients undergoing PD are managed as outpatients. It is better to leave them at home. PD patients do telehealth unless they have a special clinical situation." (Male, 40-49 age group, Colombia).* *"We have much fewer complications in PD" (Female, 50-59 age group, Chile).* *"Patients on PD dialyze at home without risk to other patients nearby." (Male, 40-49 age, Colombia).*
Shifting focus on preventing syndemics	*"Two young patients with COVID are hospitalized, one of whom is obese. Obese patients have a lower chance of recovery than those with an abnormal BMI " (Female, 40-49 age group, Mexico).* *“Chronic people are often at risk of developing complications from COVID. Unfortunately, no matter what the vaccine does, there may still be another virus next year. The world is treating the symptoms of this pandemic, but not the causes of this syndemic" (Male, 60-69 age group, Chile).* *"The world has lost a considerable number of people. We have to lead a healthy lifestyle as we are more vulnerable than we think". (Male, 50-59 age group, Chile).*

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Chapter 4: Outcomes for clinical trials involving adults with chronic kidney disease: a multinational Delphi survey involving patients, caregivers and health professionals

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This chapter is structured as per the journal article.

4.1 Abstract

Background: Many outcomes of high priority to patients and clinicians are infrequently and inconsistently reported across trials in chronic kidney disease (CKD), which generates research waste and limits evidence-informed decision making. We aimed to generate consensus among patients/caregivers and health professionals on critically important outcomes for trials in CKD prior to kidney failure and the need for kidney replacement therapy, and to describe the reasons for their choices.

Methods: This was an online two-round international Delphi survey. Adult patients with CKD (all stages and diagnoses), caregivers and health professionals who could read English, Spanish or French were eligible. Participants rated the importance of outcomes using a Likert scale (7–9 indicating critical importance) and a Best–Worst Scale. The scores for the two groups were assessed to determine absolute and relative importance. Comments were analysed thematically.

Results: In total, 1399 participants from 73 countries completed Round 1 of the Delphi survey, including 628 (45%) patients/caregivers and 771 (55%) health professionals. In Round 2, 790 participants (56% response rate) from 63 countries completed the survey includ- ing 383 (48%) patients/caregivers and 407 (52%) health professionals. The overall top five outcomes were: kidney function, need for dialysis/transplant, life participation, cardiovascular disease and death. In the final round, patients/caregivers indicated higher scores for most outcomes (17/22 outcomes), and health professionals gave higher priority to mortality, hospitalization and cardiovascular disease (mean difference >0.3). Consensus was based upon the two groups yielding median scores of ≥7 and mean scores >7, and the proportions of both groups rating the outcome as 'critically important' being >50%. Four themes reflected the reasons for their priorities: imminent threat of a health catastrophe,

signifying diminishing capacities, ability to self-manage and cope, and tangible and direct consequences.

Conclusion: Across trials in CKD, the outcomes of highest priority to patients, caregivers and health professionals were kidney func- tion, need for dialysis/transplant, life participation, cardiovascular disease and death.

4.2 Introduction

Chronic kidney disease (CKD) is associated with an increased risk of mortality, cardiovascular events, hospitalization, and progression to kidney failure(1). Patients with CKD may also experience impaired quality of life and mental health, which could be attributed in part to uremic symptoms, as well as with the shock of the diagnosis and prognostic uncertainty. As such, the management of patients with CKD can be complex and patient-cantered decision-making is needed. However, the outcomes reported across trials in CKD are highly variable and often do not include outcomes that are meaningful to patients(2).

In trials in CKD, biochemical outcomes are most frequently selected because they are more feasible to measure(3). Systematic reviews have repeatedly shown that the outcomes reported are highly heterogeneous(4-7). Life participation, fatigue, depression, and anxiety, which have been identified as high priority outcomes among patients with CKD and their caregivers are largely absent from trials in CKD(8). The omission of patient-reported outcomes in trials can limit shared decision-making, patient-provider communication, and self-management(9). The problems with outcome reporting highlights the need to identify critically important outcomes for trials in CKD.

The Standardized Outcomes in Nephrology (SONG) initiative has involved over 10 000 patients, caregivers, and health professionals in establishing core outcomes for various treatment modalities e.g., haemodialysis (10) and specific causes of CKD e.g., glomerular disease. Core outcomes are a minimum that should be measured and reported in all clinical trials conducted in people with a specific condition (11). This enables comparison of the effect of different interventions based on outcomes of critical importance to patients/caregivers and health professionals. Researchers can add other outcomes that are relevant to the intervention. As part of the SONG-Chronic Kidney Disease (SONG-CKD) project, this study aims to generate consensus among patients/caregivers and health professionals on critically important outcome domains for trials in CKD prior to the need for KRT(2), and to describe the reasons for their choices. This will be used to generate a core outcome set, to increase the value of trial evidence for shared decision-making in CKD.

4.3 Materials and Methods

Context and Study Design

The Delphi technique is recommended by the Core Outcome Measures in Effectiveness Trials (COMET) initiative to establish consensus on critically important outcomes for trials(11). As consensus was reached by round 2 in prior Delphi survey studies (12-14) we conducted two rounds with additional rounds if required. The survey was conducted online in three languages (English, Spanish and French). The SONG-CKD Delphi Technique is shown in Supplementary Figure 1.

Patients aged over 18 years with CKD (all stages and diagnoses), caregivers and health professionals, who could read English, Spanish, or French were eligible. Health professionals included physicians, nurses, allied health professionals, researchers, policymakers, regulators, and industry representatives. Regulators and industry representatives were included as health professionals because Both are relevant stakeholder groups and fit the WHO definition of health professional: "Health professionals study, diagnose, treat and prevent human illness, injury and other physical and mental impairments in accordance with the needs of the populations they serve. They advise on or apply preventive and curative measures, and promote health with the ultimate goal of meeting the health needs and expectations of individuals and populations, and improving population health outcomes. They also conduct research and improve or develop concepts, theories and operational methods to advance evidence-based health care" (15).

Multiple recruitment strategies were used to include a wide diversity of participants. Patients were recruited from hospitals, patient/consumer organizations, the SONG database, and social media. Health professionals were recruited through the SONG database, investigator networks and professional organizations. Participants received an email invitation after registering their email on the SONG website (www.songinitiative.org). Ethics approval was provided by the University of Sydney (2015-228) and participating institutions.

Data extraction and analysis

Selection of outcome domains: We included outcomes reported in systematic reviews, CKD trials, those identified in a nominal group technique study with patients/caregivers(8). We provided a plain language definition for each outcome (Supplementary Table S1) and

randomized the order of outcomes. The SONG-CKD Steering Group and investigators reviewed the list of outcomes for completeness, and the survey was piloted among 20 health professionals and patients/caregivers. The survey was administered using Qualtrics *(Qualtrics software, Provo, UT, United States)* from July 2020 to February 2021. The English survey was translated into Spanish and French by a bilingual health professional, cross-checked by a second bilingual professional and piloted with five patients/health professionals.

Round 1: Participants rated the importance of 33 outcome domains using a 9-point Likert scale based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE). Patients were asked to reflect on the importance of outcomes for all trials in CKD (prior to kidney failure and the need for kidney replacement therapy). Scores 1-3 indicated "limited importance", 4-6 indicated "important but not critical" and 7-9 indicated "critical importance". An option of "unsure" was provided. Participants could enter comments for each outcome in free-text boxes and could suggest new outcomes. New outcomes suggested by more than 10% of participants were eligible to be included in the next round. Outcomes were included in Round 2 if they had a mean ≥7 and a median ≥7 and at least 50% of participants within a stakeholder group ranked the outcome as critically important(8) (Supplementary Table S5).

Round 2: In Round 2, 23 outcomes were included. Respondents can reflect on the results of previous rounds including their own responses to develop a consensus view (16). Participants were shown their own scores from Round one, as well as the distribution of scores from patients/caregivers, health professionals in a histogram (with written explanation). Participants were asked to read and reflect on the participant comments provided in Round 1 and re-rated the outcomes again using the 9-point Likert scale and to provide further free text

responses. A Best-Worst Scale (BWS) survey which is a type of discrete choice experiment, was included to determine the relative importance of the round 2 outcomes. In the BWS survey, participants were asked to select the most and least important outcome from a series a choice sets, each consisting of four of the 23 possible outcomes. The BWS survey was constructed using a partially balanced incomplete block design with 42 choice sets split into 7 blocks of 6 choices. Participants were randomly allocated to one of the 7 blocks.

Quantitative analysis: For both rounds, we calculated the mean score, median score, and percent of participants who considered the outcome critically important (i.e., 7-9) for patients/caregivers and health professionals. A multinomial logistic regression model was used to determine the relative importance based on the Best-Worst choice tasks. Utility functions containing all outcomes and interaction terms for participant characteristics were constructed for the Best-Worst choice tasks. Following this approach, the mean regression coefficients of this function provided the relative importance scores for each outcome. As the regression coefficients have the same underlying scale, preference scores were able to be adjusted to any convenient scale. In this survey, a scale of 0 (least important) to 1 (most important) was used. Statistical analyses were undertaken using SPSS (*IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY*), Excel (*Microsoft Corporation, Product version 16.0*), and NLOGIT V6 *(Econometric Software Inc.)* for the BWS. A p-value of less than 0.05 was considered statistically significant.

Definition of consensus: Since the distribution of scores was unknown, the criteria for consensus on the critically important core outcomes could not be pre-determined. We sought to identify three to five outcomes that were critically important to patients/caregivers and health professionals, which we defined as both patient/caregiver and health professionals

yielding median scores of ≥7 and mean scores ≥7, as well as the proportions of both stakeholder groups rating the outcome as 'critically important' being greater than 50%. The SONG-CKD Steering Group approved these thresholds. We examined the BWS scores to assess differences in priorities between patients/caregivers and health professionals.

Qualitative analysis: We imported all free-text comments into HyperRESEARCH (*version 4.0.3, ResearchWare Inc., Randolph, MA*) software for data analysis. Using thematic analysis, we inductively identified concepts focusing on the reasons for their priorities, including changes in the scores and differences between stakeholder groups. Investigator (AMG) conducted thematic analysis. A second investigator (AJ) read the qualitative data to ensure that the themes captured all the data.

4.4 Results

Participant characteristics: In total, 1,399 participants from 73 countries completed Round 1 of the Delphi survey including 628 (45%) patients/caregivers and 771 (55%) health professionals. In Round 2, 790 participants (56% response rate) from 63 countries completed the survey including 383 (48%) patients/caregivers and 407 (52%) health professionals. Characteristics of patients/caregivers and health professionals are shown in Tables 1 and 2 respectively.

Of the 348 patients who completed Round 2, 171 (49%) had abnormal kidney function but were not on dialysis or transplant, 69 (20%) received a kidney transplant (deceased donor), 31 (9%) had a kidney transplant (living donor), 29 (8%) were on haemodialysis, 27 (8%) considered their kidney functions as normal, and 14 (4%) were on peritoneal dialysis.

Patient/caregiver participants were from the United States (134, 35%), United Kingdom (100, 26%), Australia (55, 14%), France (14, 4%), Spain (10, 3%), Chile (9, 2%) and 28 other countries (Table 1).

Health professionals in Round 2 included 261 (64%) nephrologists, 52 (13%) nurses, and 41 (10%) researchers. Other stakeholders included dietitians, industry, pharmacists, surgeons, general practitioners, psychologists, social workers. Health professionals were from Australia (66, 16%), United States (49, 12%), France (42, 10%), United Kingdom (42, 10%), Mexico (23, 6%) and 63 other countries (Table 2).

Likert scores

Round 1: The mean and median scores, and proportion of participants rating the outcome as 7 to 9 (critical importance) on the Likert scale for each of the 33 outcomes are provided in Table S2. The top five outcomes rated by patients/caregivers were: need for dialysis/transplant (mean score: 8.2), kidney function (8.2), blood pressure (7.8), death (7.7) and life participation (7.7). The top 5 outcomes for health professionals were: need for dialysis/transplant (8.3), death (8.1), cardiovascular disease (7.9), kidney function (7.9) and life participation (7.6). Ten outcomes did not meet the criteria for inclusion into the final round and were excluded from round 2.

Round 2: Twenty-three outcomes were included in Round 2 (Table S3). The top five outcomes rated by patients/caregivers were: kidney function (mean score: 8.2), need for dialysis/transplant (8.2), life participation (7.8), blood pressure (7.7) and cardiovascular disease (7.7). The Round 2 mean scores of patients/caregivers and health professionals by language (English, Spanish and French) are provided in Table S4. The top 5 outcomes for

health professionals were: need for dialysis/transplant (8.3), death (8.1), kidney function (7.9), cardiovascular disease (7.9) and life participation (7.6). In the Supplementary Figure S2 we provide a subgroup analysis of mean Likert scores of patients and caregivers by CKD treatment stage, diabetes, gender, age and country.

Changes in scores from round 1 to 2 within stakeholder groups

Figures 1 and 2 show the mean scores for rounds 1 and 2 for patients and caregivers and health professionals. For both stakeholder groups, mean scores were relatively stable between the two rounds. Patients/caregivers rated the following outcomes higher in Round 2: fatigue (mean score difference, 0.34), memory/cognition (0.33), and life participation (0.32). For health professionals, mean scores increased for the following outcomes between rounds 1 and 2: life participation (mean score difference: 0.38), kidney function (0.33) and need for dialysis/transplant (0.30).

Differences between stakeholder groups

Based on the difference in mean scores in the final round, 17 outcomes were rated higher by patients/caregivers (Figure 3). The greatest difference in scores were for calcium, phosphate or parathyroid hormone (absolute mean difference, 0.67) protein in the urine (0.66), and anemia (0.56). Six outcomes were rated higher by health professionals: death (0.67), hospitalization (0.35), cardiovascular disease (0.35) and depression (0.21), financial impact (0.19), need for dialysis/transplant (0.13).

Best worst scale

The relative importance of the outcomes determined from the BWS survey are shown in Figure 4. The two most important outcomes for patients/caregivers were kidney function and dialysis/transplant with similar preference scores of 1.00 (95%CI 0.0.89 to 1.11) and 0.98 (95%CI 0.87 to1.08) respectively indicating little or no difference in importance. The two most important outcomes for health professionals were dialysis/transplant and death with preference scores of 0.95 (95%CI 0.85 to 1.05) and 0.87 (95%CI 0.78 to 0.97) respectively. Of note patients/caregivers considered death to be substantially less important than health professionals with a preference score of 0.53 (95%CI 0.43 to 0.63) and less important than cardiovascular disease (0.82, 95%CI 0.72 to 0.92) and similar importance to life participation (0.56, 95%CI 0.46 to 0.66). Other notable differences between patients/caregivers and health professionals were pain (0.53, 95%CI 0.43 to 0.62 compared to 0.34, 95%CI 0.25 to 0.0.43), infection (0.53, 95%CI 0.43 to 0.62 compared to 0.33, 95%CI 0.24 to 0.42), anemia (0.49, 95%CI 0.38 to 0.60 compared to 0.13, 95%CI 0.03 to 0.23), potassium (0.34, 95%CI 0.24 to 0.44 compared to 0.07, 95%CI -0.02 to 0.17) and calcium (0.29, 95%CI 0.0.20 to 0.39 compared to 0.02, 95%CI -0.07 to 0.11).

Themes from comments

Four themes reflected the reasons, changes, and differences in outcome ratings which are described below, and the outcome related to the quote is indicated in parenthesis. Selected quotations for each theme are provided in Table 3.

Imminent threat of a health catastrophe

Terrified about the need for dialysis: Participants were worried about the potential need for dialysis underpinned the higher priority given to the need for dialysis — *"second only to death, or maybe even ahead of it, [need for dialysis] is the most feared outcome of CKD (e.g., need for dialysis)."*

Confronting death: Participants believed kidney failure meant potential deterioration of health —*"CKD leads to ESRD, which is a life-limiting condition"* and for some CKD meant impending death —*This [kidney disease] is what will probably kill me (e.g., death)."*

Accelerating decline of kidney function: Blood pressure, specifically hypertension, was considered important because it could cause rapid decline of kidney function—*"untreated or uncontrolled HBP is a major risk factor for making CKD proceed more rapidly (e.g., blood pressure)."*

Signifying diminishing capacities

Depletion and deterioration/impairing daily functioning: Outcomes that signified physical deterioration, including fatigue, life participation, and anaemia were given high priority by patients and caregivers—*" I struggle at times to commit to anything besides work as I am unsure how tired I will feel (e.g., fatigue)."* They felt diminished capacity to do everyday activities —*"It is so frustrating to see my apartment so messy but unable to do anything (e.g., life participation)".*

Distress of losing control: Hospitalization was an outcome better ranked by health professionals and according to them it is essential to restore *"patients' ability to feel that they*

are in control of their health". Physical function, however, was higher by patients and caregiver and they considered that physical function improves all aspects of well-being and stated—*"physical activity is an area in which I feel that I can regain control of my life (e.g., physical function)."*

Exacerbating burden on family: Concerns about the impact of CKD on their families explained the higher priority given to outcomes such as financial impact, —*" this disease that our son suffers from has almost cost us our home, family and future (e.g., impact on family)."*

Ability to self-manage and cope

Striving to halt disease progression: Patients wanted to know about indicators of progression of CKD to prevent deterioration so they could manage them through lifestyle changes, and the ability to track their health motivated and supported self-management *"graphing my kidney function had helped to motivate me*" *(e.g., kidney function)."*

Enabling preparedness: Patients sought to be prepared and desired information about outcomes such as mortality and kidney function so they could be more aware and set up strategies to minimize their risk of disease progression and perceived kidney function as a "*measure of kidney health*". Mentioning education and knowledge about kidney functions would allow them to become partners in their care and make healthy lifestyle decisions.

Changing and protecting lifestyle: Patients and caregivers rated biomarkers such as potassium and protein in the urine higher than health professionals because they believed

these outcomes could be modified through diet and lifestyle. For example, *—"having to limit foods that most people would consider "healthy" is exasperating (e.g., potassium)."*

Tangible and direct consequences

Minimal impact and awareness: Patients and caregivers gave lower priority to outcomes because they were *"unaware of these diseases (e.g., bone disease)"* and therefore *"did not perceive the disease as a problem."* Participants emphasized the need to focus on maximizing quality of life and asked, *"how can people with CKD live the life they want to live?"*

4.5 Discussion

Patients, caregivers, and health professionals ranked kidney function, need for dialysis/transplant, life participation, cardiovascular disease, and death as the five most important outcome domains
for trials in CKD. Among the patient-reported outcomes, life participation was rated the highest by all stakeholders. The severe, life limiting consequences and burden on the overall health and well-being of patients and their family members were reasons given for the importance attached to these outcomes. In the context of CKD, the fear and uncertainty of disease progression and possibility of requiring dialysis or kidney transplant meant that patients/caregivers emphasized the strong relevance of kidney function and other parameters, including blood pressure, that they believed could control to slow progression to kidney failure. Compared with healthcare professionals, patients/caregivers gave a much lower priority to death which was of similar importance to life participation, pain, and infection and substantially lower than kidney function or dialysis/transplant. Patients also gave higher priorities to anemia, potassium, and calcium compared to healthcare professionals. However,

it was evident from the qualitative data that patients/caregivers equate kidney function with kidney failure (leading to dialysis or transplant), whereas healthcare professionals place lower importance on kidney function.

Kidney health outcomes including kidney function and kidney failure requiring dialysis or transplantation were of critical importance to patients/caregivers and health professionals. Abnormal kidney function is associated with an increased risk of mortality, cardiovascular disease (including cardiovascular mortality) and reduced quality of life(17). Cognitive dysfunction and bone health also correlate with abnormal kidney function(18). For patients, kidney function is perceived as an outcome they can monitor to gauge their kidney health and inform treatment strategies. There is a 13-fold increase in the risk of dying from CKD than kidney failure in older adults with CKD than progress to kidney failure requiring kidney replacement therapy (19)and patients have reported anxiety, distress, and fear about disease progression, and many are reluctant to commence dialysis because of the painful, intrusive and intensive nature of the therapy(8).

Patients and caregivers gave higher priority to many patient-reported outcomes, including life participation, fatigue, sleep, physical function, and cognitive function, compared to health professionals. Some of the outcomes of high priority such as mortality and cardiovascular disease were similar to those identified to be critically important for trials in other stages of CKD including haemodialysis (14). Life participation has been established as a trial core outcome for kidney transplantation, peritoneal dialysis, glomerular disease, and children with CKD (20) (21) (22) (23) and is an indicator of the patient's capacity to participate in meaningful activities of life, which can help to maintain overall mental health and quality of life. Patients with early stages of CKD have impaired sleep quality(24), and they perceive

that sleep has minimal relevance in the treatment. Impaired cognitive function and physical performance are important factors that impact the lives of people with CKD(25) Patients reported that fatigue is associated with death, dialysis initiation, and hospitalisation and mentioned they did not realise how fatigued they were until they commenced dialysis and could compare their energy levels. Approximately 70% of patients with CKD report fatigue, with up to 25% reporting severe symptoms(26).

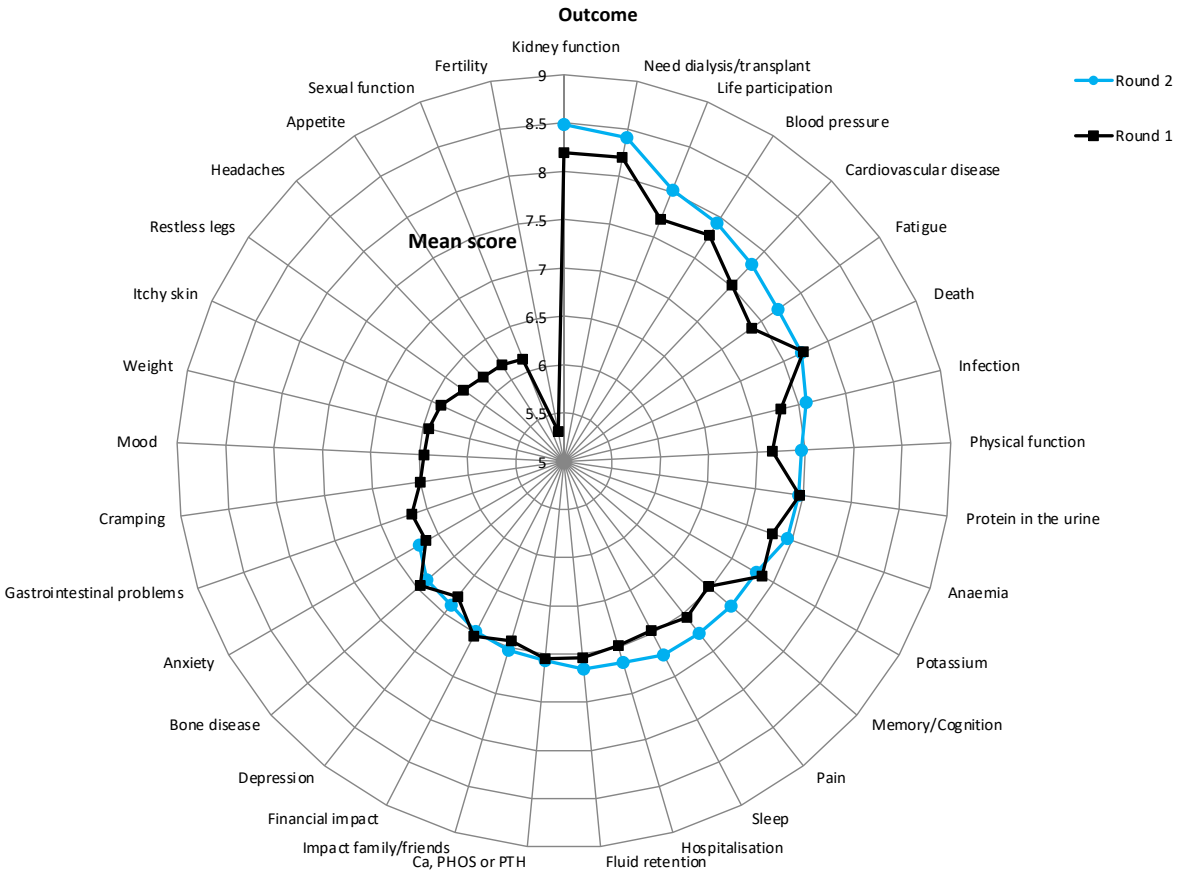
Our survey, conducted in three languages, included a large and broad range of stakeholders from 73 countries, with patients/caregivers comprising almost half of the sample. We achieved diversity in terms of demographic and clinical characteristics, including causes and stages of CKD. The proportion of the respondent group changed between the two rounds. Also, most of the respondents in the health professional group were nephrologists and nurses, which may be because they are the main clinicians involved in the care of patients with CKD. Using both a quantitative and qualitative approach, we generated robust estimates of absolute and relative priorities and identified reasons for the different priorities. The retention rate was reasonable based on previous Delphi surveys to establish core outcomes (12) (27). However, we acknowledge some potential limitations. Most participants were from high income countries. The proportion of participants who completed the survey in French (n = 71) and Spanish (n = 56) was relatively low compared with the English (n = 663). Whilst the online mode of administration enabled broader participation, this would have precluded the involvement of those without access to the internet or with limited computer literacy. Patient-reported outcome measures are increasingly being implemented in research in CKD. In early CKD, patient-reported outcomes such as fatigue, financial impact, sleep physical function, pain, appetite, mood, cramping, and restless legs, have also been identified as being important

to patients. We suggest that these should also be considered in trials in patients with early CKD.

Kidney function, need for dialysis or transplant, life participation, cardiovascular disease, death were highly prioritized by patients, caregivers and health professionals. In selecting the core outcomes, feasibility for implementation in all trials and acceptability (e.g. respondent burden), will be considered. These outcomes will be discussed at a SONG-CKD consensus workshop to finalize the core set of outcomes to be reported in all trials in CKD, noting that other outcomes may be selected by the trial investigators for specific trials. Further work will be conducted to establish a core outcome measures for each of the core outcome domains. Consistent reporting of critically important outcomes across trials in CKD will enhance the value of the evidence base to support shared decision making, patient-cantered care and improve patient-important outcomes.

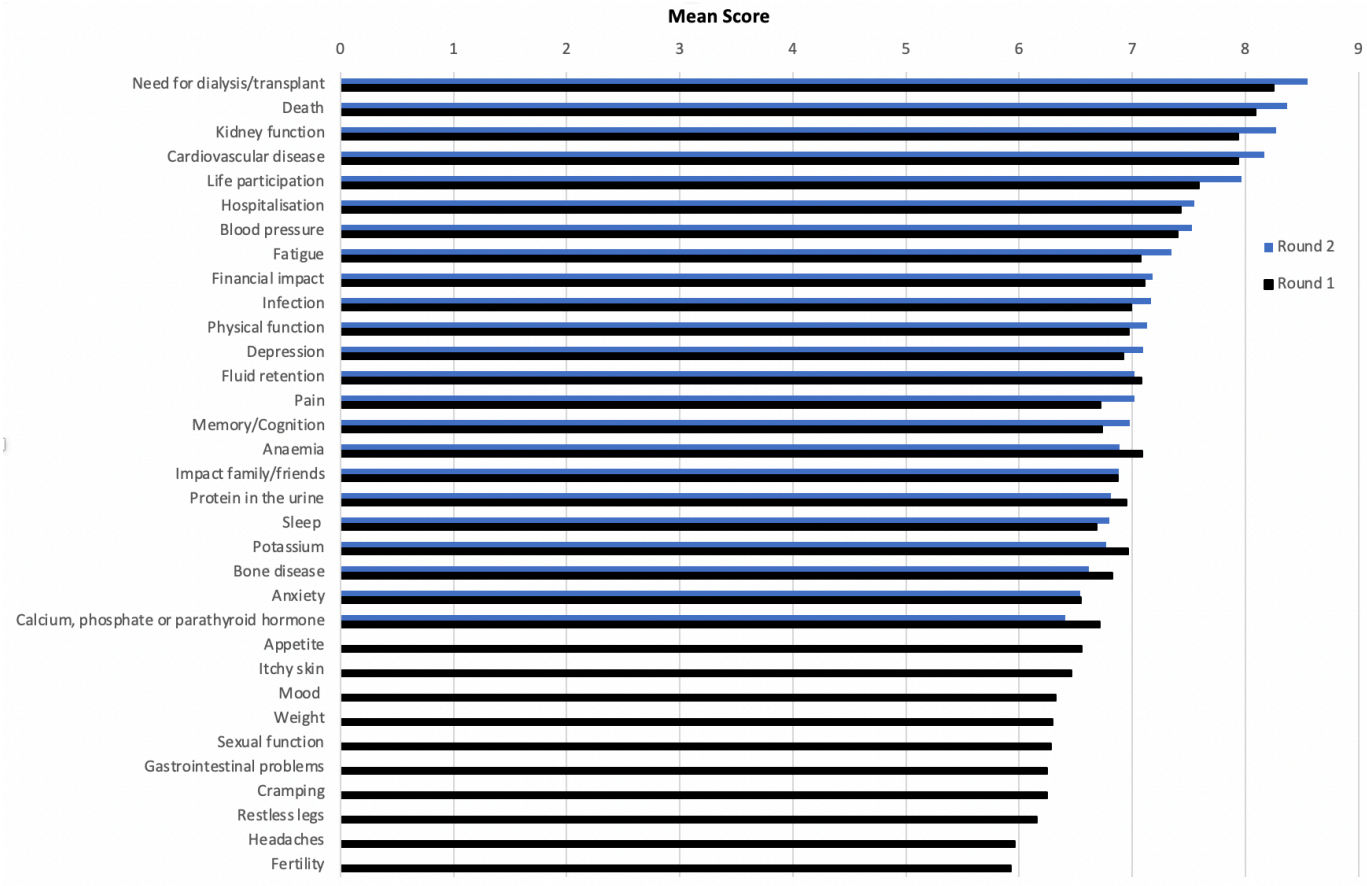
Acknowledgements

We thank all the patients and family members who gave their time to participate in the study.



Note: Ordered by round 2 scores. Round 1 (n=628); round 2 (n=383). Mean scores for round 2 are not available for outcomes that were excluded in those rounds.

Figure 4.1 Mean Likert scores (9-point scale) of all outcomes for patients and caregivers in Delphi survey rounds 1 and 2



Note: Ordered by round 2 scores. Round 1 (n=771); round 2 (n=407). Mean scores for round 2 are not available for outcomes that were excluded in those rounds.

Figure 4.2 Mean Likert scores (9-point scale) of all outcomes for health care professionals in Delphi survey rounds 1 and 2

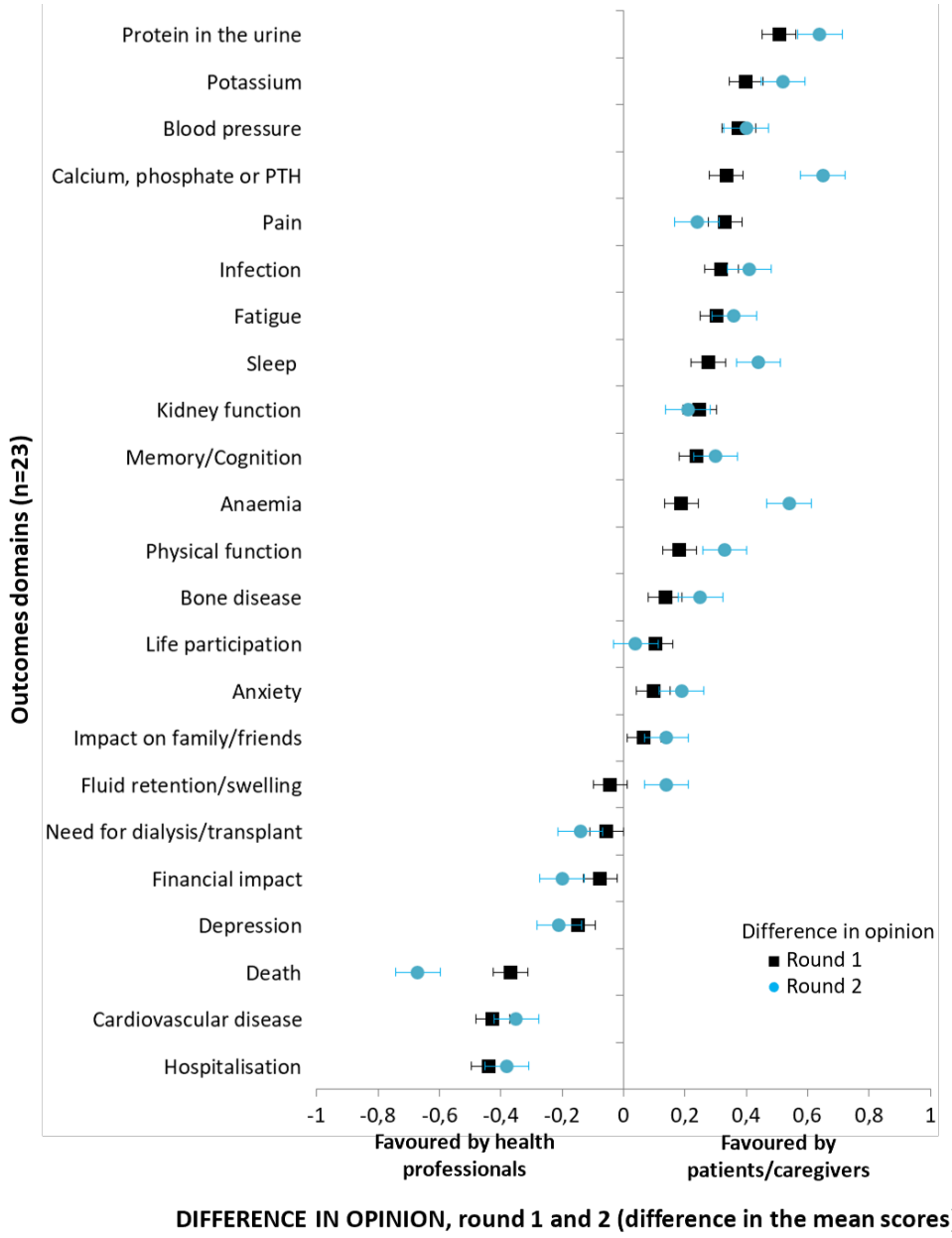


Figure 4.3 Differences in the mean Likert scores between patients/caregivers and healthcare professionals (error bars refer to 95% confidence interval)

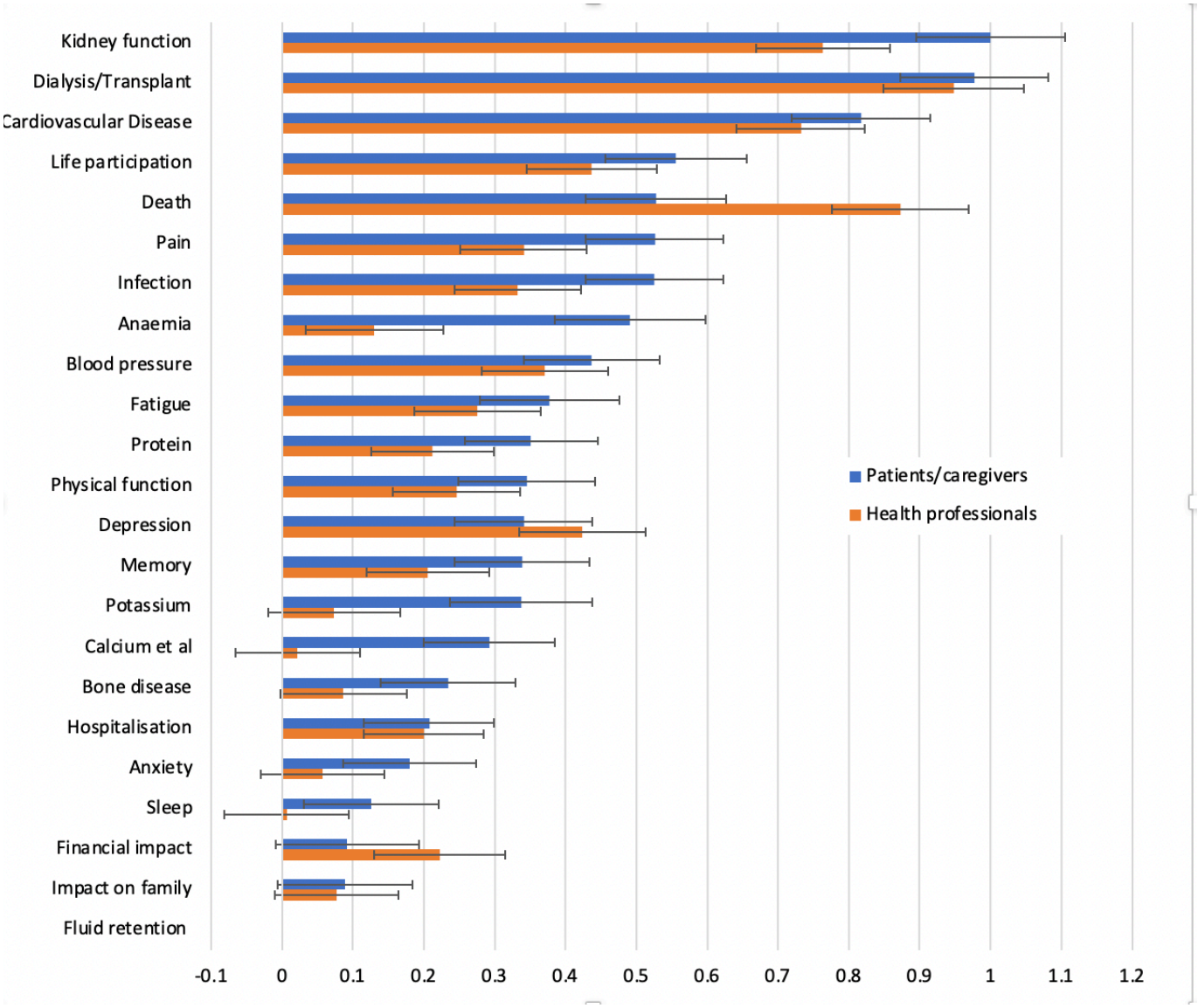


Figure 4.4 The relative importance score of outcomes from the best–worst scale survey for patients and caregivers, and health care professionals

Table 4.1 Characteristics of patients/caregivers

Characteristic	Round 1 (n=628)	Round 2 (n=383)
Participant type [a]		
Patient	570 (91%)	348 (91%)
Caregiver/family member	83 (13%)	53 (14%)
Gender [b]		
Female	375 (60%)	232 (61%)
Male	242 (39%)	145 (38%)
Age group (years)		
18-30	23 (4%)	8 (2%)
31-50	179 (28%)	100 (28%)
51-70	314 (50%)	204 (53%)
71 and over	112 (17%)	71 (18%)
Employment status [c]		
Retired/ Not employed	301 (49%)	188 (49%)
Full time/Part time/casual	270 (44%)	168 (44%)
Student	11 (2%)	6 (2%)
Education		
Did not complete high school	55 (9%)	39 (10%)
High school graduate	68 (11%)	37 (10%)
Higher education	485 (79%)	307 (80%)
Kidney function [d] **and/or treatment** [e] (patients only)		
Abnormal kidney function but no dialysis or transplant	278 (49%)	171 (49%)
Kidney transplant recipients (deceased donor and living	140 (24%)	100 (29%)
Dialysis (haemodialysis and peritoneal dialysis)	84(15%)	43 (12%)
Cause of kidney disease [f] (patients only)		
Polycystic kidney disease	179 (31%)	123 (35%)
Glomerulonephritis	63 (11%)	42 (12%)
Hypertension	65 (11%)	36 (10%)
Type 2 Diabetes	33 (6%)	17 (5%)
Type 1 Diabetes	13 (2%)	8 (2%)
Relationship to the patient (carers only)		
Parent	35 (43%)	12 (23%)
Spouse/partner	23 (28%)	29 (55%)
Child	13 (16%)	6 (11%)
Country		
United States	244 (39%)	134 (35%)
United Kingdom	136 (22%)	100 (26%)
Australia	82 (13%)	55 (14%)
Canada	21 (3%)	17 (4%)
France	20 (3%)	14 (4%)
Other [g]	42 (7%)	26 (7%)

CKD, Chronic Kidney Disease. eGFR, Estimated Glomerular Filtration Rate. [a] Some have multiple roles, employment status, ethnicities, treatments and health conditions; [b] Gender: Other: Round 1:11 (2%) Round 2:6 (2%;)[c] Employment status: Other Round 1: 54 (9%) Round 2: 34 (9%); [d] Stage of CKD (Rd 1 n=339, Rd 2 n=204) Excludes patients on dialysis or transplant; Stage 1 (normal or high eGFR of 90 or more) 17(5%)13 (6%) Stage 2 (mild CKD, eGFR 60-89) 36 (11%) 26 (13%) Stage 3 (moderate CKD, eGFR 30-59) 146 (43%) 85 (42%) Stage 4 (severe CKD, eGFR 15-29) Round 1: 85 (25%) Round 2: 49 (24%) Stage 5 (eGFR <15) without dialysis or transplant Round 1: 29 (9%) Round 2: 19 (9%) I don't know 26 (8%) 12 (6%) Kidney function and/or treatment: My kidney function is normal: Round 1: 46 (8%) Round 2: 27 (8%) I do not know: Round 1: 18 (3%) Round 2: 9 (3%) [e] Excludes patients on dialysis and transplant Cause of kidney disease (patients only) I do not know: Round 1: 82 (14%) Round 2:39 (11%) Drug induced/ Other: Round 1: 166 (29%) Round 2: 102 (30%) [g] Other includes 29 countries (in descending order of number of participants): Spain, Chile, Denmark, Ireland, Mexico, India, New Zealand, Belgium, Republic of Korea (South), Hong Kong (S.A.R.), Italy, Netherlands, Argentina, Germany, Greece, Hungary, Malaysia, Morocco, Nicaragua, Norway, Poland, Singapore, Slovenia, South Africa, Switzerland, United Arab Emirates, Uruguay and Taiwan (Republic of China). Concomitant conditions (patients only) Hypertension (high blood pressure) Round 1: 364 (64%) Round 2: 221 (64%) Type 2 Diabetes Round 1: 78 (14%) Round 2: 47 (14%) Type 1 Diabetes Round 1: 23 (4%) Round 2: 13 (4%) None Round 1: 156 (27%) Round 2: 100 (29%)

Table 4.2 Characteristics of health professionals

Characteristic	Round 1 (n=771)	Round 2 (n=407)
Participant type [a]		
Nephrologist	431 (56%)	261 (64%)
Nurse	109 (8%)	52 (13%)
Researcher	60 (4%)	41 (10%)
Dietitian	29 (2%)	11 (3%)
Industry	13 (1%)	10 (2%)
Pharmacist	9 (1%)	7 (2%)
Surgeon	20 (1%)	6 (1%)
General practitioner	31 (2%)	2 (0.5%)
Psychologist	6 (0.4%)	2 (0.5%)
Social worker	5 (0.4%)	2 (0.5%)
Policy maker	2 (0.1%)	0
Other	118 (8.4%)	55 (14%)
Gender		
Male	379 (49%)	211 (52%)
Female	375 (49%)	188 (46%)
Other	17 (2%)	8 (2%)
Age group (years)		
18-30	115 (15%)	15 (4%)
31-40	173 (22%)	85 (21%)
41-50	194 (25%)	110 (27%)
51-60	160 (21%)	110 (27%)
61-70	102 (13%)	68 (17%)
71-80	24 (3%)	17 (4%)
> 81	3 (0.4%)	2 (1%)
Experience in nephrology (years)		
≤10	245 (18%)	90 (11%)
11-20	205 (15%)	118 (15%)
21-30	165 (12%)	114 (14%)
>30	137 (10%)	95 (12%)
Not applicable	81 (6%)	32 (4%)
Number of CKD trials as investigator		
0	269 (19%)	114 (14%
1-5	265 (19%)	150 (19%)
6-10	86 (6%)	62 (8%)
11-15	27 (2%)	20 (3%)
>15	61 (4%)	42 (5%)
Not applicable	125 (9%)	61 (8%)
Country		
Australia	91 (12%)	66 (16%)
United States	77 (10%)	49 (12%)
France	71 (9%)	42 (10%)
United Kingdom	59 (8%)	42 (10%)
Canada	52 (7%)	39 (10%)
Mexico	174 (23%)	23 (6%)
New Zealand	14 (2%)	10 (2%)
India	14 (2%)	8 (2%)
Belgium	12 (2%)	8 (2%)
Italy	11 (1%)	8 (2%)
Brazil	11 (1%)	7 (2%)
Chile	23 (3%)	3 (1%)
Other [b]	162 (21%)	102 (25%)

Abbreviation: CKD, Chronic Kidney Disease.

[a] Some have multiple roles.

[b] Other includes 56 countries (in descending order of number of participants): Spain, Hong Kong (S.A.R.), Netherlands, Germany, Nigeria, Saudi Arabia, Uruguay, Argentina, China, Japan, Switzerland, Colombia, Egypt, Malaysia, Peru, Portugal, Romania, Sweden, Austria, Lithuania, Nepal, Pakistan, Poland, Russian Federation, Singapore, South Africa, Sudan, Bangladesh, Bolivia, Chad, Republic of Korea (South), Denmark, Greece, Israel, Turkey, Armenia, Belarus, Bulgaria, Cameroon, Republic of the Congo, Croatia, Czech Republic, Ethiopia, Finland, Jordan, Mongolia, Myanmar, Norway, Slovakia, Sri Lanka, Thailand, Bolivarian Republic of Venezuela, Viet Nam, Zimbabwe, Tanzania, Taiwan (Republic of China).

Table 4.3 Selected illustrative quotations

Theme	Quotations
Imminent threat of a health catastrophe	
Terrified about the need for dialysis	*—Dialysis is something I think about daily, and the unknown causes much anxiety. (Need dialysis, patient)* *— I don't believe in prolonging my life beyond its natural expiration date, my quality of life will not depend on a [dialysis] machine.(Need dialysis, patient)* *— I will NOT do dialysis or have a transplant! (Need dialysis, patient)* *— There isn't much else! Death (Need dialysis, patient)* *— A major psychological hurdle and fear of the unknown (Need dialysis, caregiver)* *— Finding treatments to slow or stop the need for this option is critical. (Need dialysis, health care professional)*
Confronting death	*—As a single parent with ESRD, my family will have to pick up the responsibility of raising my child makes me quite sad. (Death, patient).* *—I knew kidney disease was a leading cause of cardiovascular disease because my father died from it (CVD, patient).* *— Nobody knows when they are going to die but when you have a long-term chronic condition it is something that is always on your mind (Death, patient)* *— If you have CKD, it will shorten your life (Death, patient)* *—Indication of ultimate failure (Death, patient)*
Accelerating decline of kidney function	*—I did not realise what an important role the kidneys played in the functioning of the human body until my kidneys failed. (KF, patient).* *— My BP has been under control with medication but i worry that as i approach end stage will medication still work -Medication also? (Blood pressure, patient)* *— Management of blood pressure is important because it can lead to other health problems (Blood pressure, health care professional)* *— By definition this is an endpoint that will happen, it is the factors that lead to this outcome that are more important that the outcome itself (Death, caregiver)*
Signifying diminishing capacities	
Depletion and deterioration/impairing daily functioning	*—I don't have the energy to dedicate myself to hobbies or projects. I have to force myself to do things (Anaemia, patient)* *—Patient should be actively involved in decision making regarding their care. (LP, health care professional)* *—Fatigue was erratic. One day I'd feel like I was dragging a car around and the next day I'd feel like I could run a marathon. It made it difficult to plan outings/events. (Fatigue, patient)* *— Fatigue affects social life, appetite, relationships and activity (Fatigue, caregiver)* *—Tired of forcing myself to do things when all I have the energy to do is read a book or go to bed. (Fatigue, patient)*
Distress of losing control	*—I intend to avoid hospitalization since it represents a loss of control for me." (Hospitalization, patient)* *—For most people this outcome is out of their control (Hospitalization, health care professional)* *—I was anxious because my disease did not progress consistently, and I never knew when I'd crash. (Anxiety, patient)*
Exacerbating burden on family	*—Whether comes a time when I'm unable to work, and I am unable to get any income protection insurance due to my condition (Financial impact, patient).* *— Family support needed " (Death, patient)* *— Now that I'm not as well as I used to, the support of the family has been key. When they weren't supportive, I feel into severe depression because they couldn't understand what I was going through. Now that they are more onboard, feels easier to me, though I know it takes a toll in their lives as well. (Impact on family, patient)* *—I believe that chronic illness is a family condition. (Impact on family, caregiver)*
Ability to self-manage and cope	
Striving to halt disease progression	*—I worked to control my protein amounts that I ate (Protein in the urine, patient).* *—it was rewarding when I was able to slow down the progression on the decline (kidney function (KF), patient).* *—The more patients know about how their kidneys work, the better able they are to become partners in their own care and make health lifestyle choices. (KF, health care professional)*

	—It never will return to your best reading prior to being diagnosed with kidney disease but you can prolong your life by being informed as much as possible. (KF, patient) *— The more effective the detection, the earlier patients and doctors can act on the issue. (KF, health care professional)* *—Basic education on kidney function is vital for patients. (KF, caregiver)*
Enabling preparedness	*—All my relatives died of kidney failure and I'd like to find out all that I can (Death, patient).* *—The kidneys do much more than I thought, and you can prolong your life by being informed as much as possible (kidney function, patient).* *—Since this run in my family i did research early on. I worked to control my protein amounts that I ate. I also worked to understand my labs. (Protein in the urine, patient)* *—What do people want to do sex but can't because thinking again can't spoil the kidney therefore people gets scare of doing sex (Sexual function patient)* *—Deal with what might be catastrophic but could be treatable" (CV, patient)*
Changing and protecting lifestyle	*—I began to eat vegan with the help of a dietitian, and it stabilized the protein in the urine (protein in the urine, patient)* *—This has been my biggest issue - I'm in early CKD stage 5 now, just not on dialysis yet. (Potassium, patient))* *—The earlier the diagnosis the earlier dietary and other life changes could be made to improve quality of life and longevity (KF, patient)* *—Fatigue is still my biggest problem, but I still push myself o get out for a walk and garden (Physical function, patient)* *—Controlling demands usually a strict diet, sometimes meds. It can be controlled, but diet restrictions affect many patients quite much. (Potassium, health professional)*
Tangible and direct consequences	
Minimal and awareness	*—Dr has never spoken to me about sleep being affected with CKD. (Sleep, patient)* *—This does not affect me, but it seems many others are concerned about this so I am adjusting my response (Bone health, patient)* *— It´s a critical complication for those suffering it, but it is not the most common complication in CKD patients (Bone health, patient)* *— [bone health] is an important issue, similar to other outcome relating to phosphate. Fractures in later life are a big health/death risk factor. Not many patients are advised early on in CKD to take care of their bones. (Bone health, health care professional)*

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Chapter 5: A core outcome set for trials in chronic kidney disease: report of the Standardized Outcomes in Nephrology – Chronic Kidney Disease (SONG-CKD) stakeholder workshops

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This chapter is structured as per the journal article.

5.1 Abstract

The omission of outcomes of importance to patients with chronic kidney disease (CKD) and their caregivers from trials can impede decision-making based on patient-centered outcomes. As part of the global Standardized Outcomes in Nephrology – Chronic Kidney Disease (SONG-CKD) initiative, we aimed to establish a consensus-based set of core outcomes for trials in CKD (prior to the need for kidney replacement therapy). We convened two international stakeholder workshops in English and Spanish languages that involved 61 patients/caregivers and 75 health professionals from 18 countries. The results of the international Delphi survey were presented to the participants. Participants were asked to discuss and endorse the potential core outcomes (mortality, kidney function, life participation, and cardiovascular disease), and to provide suggestions for implementing the core outcomes. The discussions were summarized into four themes: reflecting a comprehensive approach to health, facilitating patient empowerment in their own care, ensuring applicability to broad geographic areas and populations, and feasibility for implementation. Patients, caregivers, and health professionals agreed that mortality, kidney function, life participation and cardiovascular disease should be established as core outcomes for trials in CKD.

5.2 Background

Across many medical disciplines, there are increasing efforts to establish core outcomes sets, defined as the minimum set of outcomes to be reported in trials in a specific population because they are identified by patients, caregivers and health professionals to be critically important for decision-making [1,2]. Core outcomes sets can improve the relevance, reliability, and comparability of trial results to support decision-making in practice and policy [1-3].

In nephrology, the global Standardized Outcomes in Nephrology (SONG) initiative commenced in 2015 and has since established core outcome sets for hemodialysis, kidney transplantation, peritoneal dialysis, children with CKD, polycystic kidney disease, and glomerular disease [4-6]. Most recently, the SONG-CKD was launched to establish core outcomes for trials in patients with CKD not requiring kidney replacement therapy. There can be large variability in the symptoms across the five stages of CKD, which may also have implications in determining core outcomes that may be common across all stages of CKD. Also, patients with CKD not yet requiring replacement therapy may also have specific concerns related to their prognosis, particularly in terms of kidney failure and the need for dialysis or transplant. Thus, it is relevant to establish a specific core outcome set for CKD. To finalize the set of core outcome domains for CKD, we convened two international multistakeholder workshops in English and Spanish language to discuss the proposed core outcomes that were identified through focus groups with nominal group technique conducted in four countries [7]. The SONG-CKD process included multinational focus groups with nominal group technique to identify potential outcomes to be included the in Delphi survey, and an international Delphi survey [8] , which collectively involved over 383 patients/caregivers and 407 health professionals from 63 countries [7] to general consensus

about critically important outcomes for trials in CKD. In this report, we summarize the discussions among patients, caregivers, and health professionals on establishing and implementing core outcomes in trials in CKD.

5.3 SONG-CKD consensus workshops

Overview and Context

The phases of SONG-CKD are presented in Supplementary Figure S1. We convened two international SONG-CKD consensus workshops by Zoom videoconference in March 2021 (in English) and October 2021 (in Spanish). The purpose of the workshops was to discuss establishing and implementing the potential core outcomes for trials in CKD (prior to the need for kidney replacement therapy), which were: mortality, kidney function, life participation, and cardiovascular disease. The four proposed core outcomes were based on the results of an international two-round Delphi survey[8], that was conducted in three languages (English, Spanish and French). The survey was completed by 790 participants from 63 countries, including 383 (48%) patients/caregivers and 407 (52%) health professionals.

Participants and contributors

We invited patients with CKD aged 18 years or older, their caregivers, and health professionals (nephrologists, researchers, allied health, regulators, funders, policy makers and industry representatives) to attend the workshop. Targeted invitations were sent to individuals holding leadership or decision-making roles in professional societies (e.g. International

Society of Nephrology (ISN), Sociedad Latino Americana de Nefrología e Hipertensión (SLANH), trial organizations (e.g. ClinicalTrials.gov), regulatory agencies (e.g. United States Food and Drug Administration (FDA), European Medicines Agency (EMA)), funders (National Institutes of Health), and guideline organization (E.g. Kidney Disease Improving Global Outcomes).

In total, 20 patients/caregivers and 42 health professionals from 12 countries attended the English workshop (n=62) and 41 patients/caregivers and 33 health professionals from nine countries attended the Spanish workshop 2 (n=74). The names and affiliations of all attendees and contributors are provided in the acknowledgements. The patients and caregivers were from Chile (n=26), Mexico (n=14), Australia (n=9), the United States (n=4), United Kingdom (n=4), Denmark (n=2), Hong Kong (n=1) and Canada (n=1). Health professionals were from 18 countries including Chile (n=17), Australia (n=15), the United States (n=9), United Kingdom (n=6), Mexico (n=5), Canada (n=3), France(n=3), Uruguay (n=2), Brazil (n=2), Germany (n=2), Hong Kong (n=2), India (n=2), and one each from Guatemala, Lebanon, Bolivia and Colombia.

Workshop program and process

Participants received the workshop program and materials prior to the workshop. During the workshops, we presented the SONG-CKD process and the results of the SONG-CKD Delphi survey[8]. In the Delphi survey that was completed by 383 patients/caregivers and 407 health professionals. Participants were allocated to 6 and 7 breakout groups for the English and Spanish workshops, respectively. Each group consisted of 8 to 12 participants including patients/caregivers and health professionals with various roles to capture diverse perspectives

and support exchange of ideas and knowledge. The groups were moderated by a trained facilitator and co-facilitator(s).

As background, we explained that a core outcomes set should consist of three to five outcome domains (including at least one patient-reported outcome) that are feasible to measure and report in all trials [9]. Participants reflected and discussed the four consensus-based critically important outcomes that were identified in the SONG-CKD Delphi survey: mortality, kidney function, life participation, and cardiovascular disease. The discussion guide and questions are provided in Supplementary file Item 1. After the breakout group discussion, the group reconvened in a plenary session and the chair (MM) called on a spokesperson from each breakout group to summarize their discussion.

All breakout group discussions and the plenary session were audio recorded and transcribed. Transcripts were entered into HyperResearch (version 4.0.3, ResearchWare Inc, Randolph, MA) to assist coding and analysis. Using thematic analysis, one investigator (AMG) read the transcripts line-by-line, and inductively identified and coded concepts into themes reflecting stakeholder perspectives that underpinned the proposed core outcomes for trials in CKD. Investigator AJ reviewed the coding. All facilitators and co-facilitators reviewed the themes to ensure that it captures the full range and depth of the discussion. All attendees and contributors were given the opportunity to provide feedback on a draft report. Any additional comments were integrated into the final report.

5.4 Summary of workshop discussions

Overview

We identified four themes that addressed the justification and implementation of the core outcomes: reflecting a comprehensive approach to health, facilitating patient empowerment in their own care, ensuring applicability to broad geographic areas and populations, and feasibility for implementation. Subthemes are described in the following section and selected quotations to support each theme are presented in Box 1. The SONG-CKD core outcome domains are shown in Figure 1 (tier 1). A summary of the key recommendations from the workshops is provided in Box 2.

Reflecting a comprehensive approach to health

Capturing life threatening complications: Participants agreed that the core outcomes should include mortality and outcomes that were life-threatening (e.g. cardiovascular disease). They recognized that the risk of cardiovascular-related death was higher for patients with CKD — *"A lot of people don't know the impact of cardiovascular disease (e.g., cardiovascular disease, patient)."*

Preventing disease progression: Progression to kidney failure requiring kidney replacement therapy was of utmost concern to patients/caregivers and health professionals. Patients and caregivers feared dialysis as it was invasive and would impair their quality of life —*"I lead a normal life as much as I can, but I'm very afraid of the progression of my kidney failure ending up in dialysis, that's why I take care of myself (e.g., kidney function, patient)."* The outcome of kidney function would allow patients/caregivers and health professionals to monitor progression of CKD.

Living a fulfilling life: Participants emphasized that the ability to live a fulfilling life and maintain quality of life with CKD should be reflected in the core outcomes set — *"It is simply enjoying life, what do you really need to feel complete*". The disease and treatment burden of CKD impaired mental health and daily functioning, which reinforced the relevance of including life participation as a core outcome—*"Participation in life is the ability to continue performing daily activities to the best of your ability despite treatment and diagnosis of chronic kidney disease (e.g., life participation, patient)."*

Protecting mental health: The shock diagnosis of CKD, the uncertain prognosis, and fears related to the potential of requiring dialysis led to anxiety, which also consequently impaired life participation – *"when I have discussions with those patients, I think they are worried about death, but the bigger worry is ending up on a dialysis machine."(e.g., life participation, patient)."* Also, patients elaborated that the despair and depression attributed to CKD could restrict life participation — *"if you're not feeling well, if you're depressed or if you've got brain fog, your life participation is going to be affected by that" (e.g., life participation, patient)* which impinged on their capacity to do and enjoy daily activities.

<u>Facilitating patient empowerment in their own care</u>

Raising awareness and improving knowledge: Participants believed that establishing the core outcomes of, for example cardiovascular disease and kidney function, promoted awareness and knowledge-seeking among patients — *"understanding the risk of how the health of your kidneys interacts with other aspects of health such as cardiovascular disease (e.g., cardiovascular disease, patient)*." A better understanding of CKD and risk of comorbidities motivated self-management, including better control of blood pressure to prevent

cardiovascular events and deterioration of kidney function — "*when a patient does not want to control their blood pressure, I always tell them that it is important because if they have a stroke, their quality of life and what they will be able to do in their life will be very different (e.g., cardiovascular disease, health professional)*."

Tracking and self-monitoring health status: Kidney function was supported as a core outcome because it enabled patients to monitor their kidney health and informed strategies for self-management, particularly with regards to medication and lifestyle changes to minimize the risk of disease progression — *"I am more organized so I can have better nutrition, health and kidney function, when you listen to the doctors, follow your treatment and check-ups (e.g., kidney function, patient)."*

Maximizing autonomy and maintaining lifestyle: Patients explained that a key goal was to remain independent and to have the capacity to do meaningful activities of daily living – *"It is important to stay involved in life as much as possible, even if it becomes more difficult every day (e.g., life participation, patient)."* They were concerned that CKD and disease progression could potentially diminish their capacity in many areas of their lives —*" Can I continue working? Can I continue doing sports? Can I continue with my life as normal?... "Being able to run a house, being able to take children to school, being able to work, go out dancing... (e.g., life participation, patient)."*

<u>Ensuring applicability to broad geographic areas and populations</u>

Implementable in different resource settings: Health professionals asserted that the core outcomes needed to be feasible for implementation in different resource settings, including in

low to middle income countries. They also stated that the patient-reported outcome of life participation was broadly relevant and could be interpreted differently depending on the region and cultural views —*"Life participation is going to be very different depending on the culture and the part of the world from which come (e.g., life participation, health professional)."*

Relevant to all types and stages of chronic kidney disease: CKD was recognized to be diverse with different causes and all diagnoses, and prognostic courses. Thus, the core outcomes had to be relevant across or diagnoses and CKD stages (i.e., 1-4, prior to the need for kidney replacement therapy) —*"The medicine that you're on between stages one and five, what are they, and are they going to affect my ability to be able to carry on doing what I was doing before?" (e.g., life participation, patient).*

Feasibility for implementation

Standardizing definitions and measures: The need to standardize the definition of the core outcomes and measures would allow for consistent reporting, and thereby enable the comparison of the effectiveness of interventions across trials. For some outcomes, such as life participation, some suggested that —*"Life participation definitely needs a new measure (e.g., life participation, patient)."* A standardized measure for life participation would have to capture all dimensions considered to be critically important for patients.

Fostering patient participation and involvement in trials: Some expected that the implementation of the core outcomes may motivate patients to participate in trials as they ensure that trials address outcomes of relevance and importance to them – *"If we want people*

to participate in research, we must answer the questions that are important to them, not necessarily the questions that are important to us (e.g., life participation, health professional"). They also stated that patients may be more inclined to be involved in the dissemination and implementation of trials that include patient-important outcomes —*"the results will certainly be adopted quite quickly due to the strong push towards patient voice representation in clinical trials (health professional)."*

Engaging triallists, industry and regulators: Buy in from all relevant stakeholders, including triallists, industry and regulators, would support widespread implementation of the core outcomes in trial*s — "need to get buy-in from people who design trials and pharmaceutical companies that develop drugs (health professional)"*

5.5 Post-workshop consultation

The draft workshop report was circulated to all participants who were requested to provide feedback within two weeks. The SONG-CKD core outcome set (Figure 1) was distributed to all participants for review and uploaded to the SONG website for general feedback and comment (https://songinitiative.org/projects/song-ckd/). The report was revised based on feedback and comments from workshop attendees and contributors.

5.6 Discussion

Mortality, kidney function, life participation, and cardiovascular disease were agreed upon by patients, caregivers, and health professionals to be included in the core outcomes set for trials in CKD, across all groups in both English and Spanish-speaking workshops, there appeared

to be consistent agreement on the core outcomes and no apparent differences by country/language were noted. Participants believed that the SONG-CKD core outcomes were comprehensive in that they encapsulated the most meaningful clinical and psychosocial impacts of CKD, would enhance patient capacities for self-management, would be relevant in diverse settings and populations and could be feasibly implemented in trials. For patients, kidney function was of critical importance to be reported in trials as this was a means to monitor progression of CKD, it motivated and informed self-management, and helped them to gain a sense of control. Stakeholders recognized that the symptoms of CKD, side effects of treatment, and anxiety (particularly about the potential need for dialysis) threatened their ability to do their usual daily activities. They believed life participation should be consistently reported in trials so patients could use the evidence for decision-making based on the goals of maintaining independence and the ability to enjoy and lead a fulfilling life.

The 61 patients and caregivers who participated in the workshops which were mainly from Chile (n=26), Mexico (n=14), Australia (n=9), the United States (n=4), United Kingdom (n=4) compared with the 628 patients and caregivers from 34 countries who participated in the Delphi survey, which was conducted prior the workshops. In total 1399 participants from 73 countries participated in the Delphi survey with 26% of patients/caregivers and 44% of health professionals bring from low- to middle-income countries.

The SONG-CKD core outcomes set (Figure 1) was established based on the workshop discussions. Mortality and cardiovascular disease were also included in the core outcomes set for adults receiving hemodialysis, peritoneal dialysis, kidney transplantation, polycystic disease and glomerular disease [4-6,10]. This may emphasize the concern of the increased risk of mortality and cardiovascular disease across diagnoses and treatment stages of CKD. Life

participation was initially identified as a core outcome for trials in kidney transplant recipients and has since been included as a core outcome also for peritoneal dialysis, glomerular disease, and children with CKD [6,11]. Across the diagnoses and treatment stages of CKD, including CKD not requiring the need for kidney replacement therapy, the outcome of life participation highlights the need to focus on minimizing the consequences and burden of CKD and its treatment to enable patients live well with CKD[11]. Of note, a SONG Life Participation measure has been developed and validated for use in kidney transplant recipients, which may be evaluated for its potential use in the CKD population [12].

Further work will be conducted to identify valid core outcomes measures for each of the core outcome domains that can be feasibly implemented in trials in patients with CKD. The uptake of core outcomes in CKD will strengthen trial-based evidence to inform decision-making based on outcomes that are relevant, meaningful and of critical importance to patients, caregivers, and health professionals.

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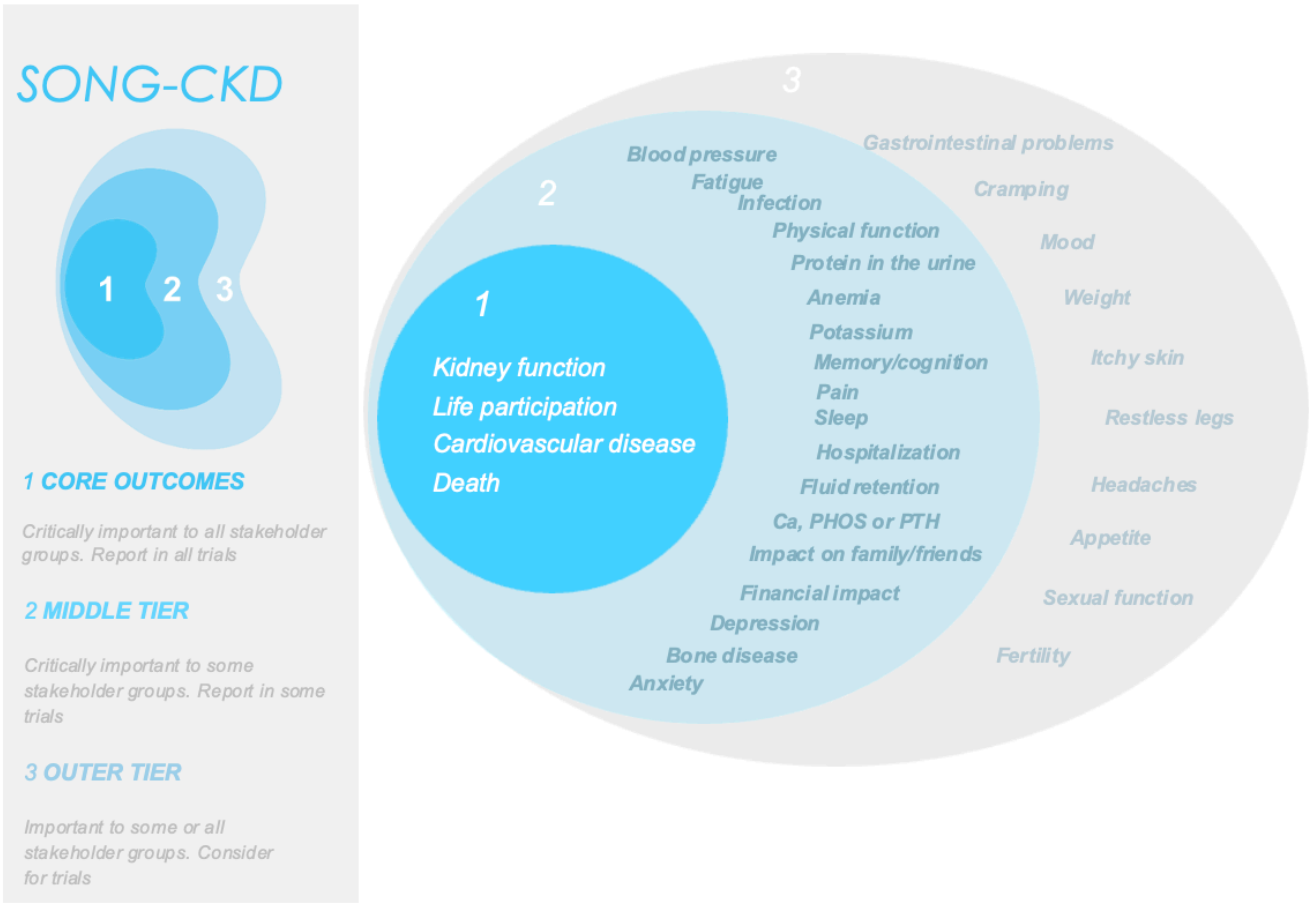

Figure 5.1 SONG-Chronic Kidney Disease (SONG-CKD) core outcome domains.

Table 5.1 Selected quotations from the workshop discussions illustrating and summarizing each theme

Theme	*Quotations*
Reflecting a comprehensive approach to health	
Capturing life threatening complications	*— "I know death means dying, but at the same time, we might look at death differently than a physician would (patient)."* *—"Honestly, I don't think about this. Doctors talk about blood pressure because the kidney affects the blood pressure, but they never really say, OH, by the way, this is going to be one that's going to affect your life later on (patient)."* *—"We wanted to distinguish, in cardiovascular disease, between heart attack and failure, and acknowledged it had a large burden on the population (patient)."* *—"You're looking for measures that currently impact on the patients, like life participation or cardiovascular disease, and measures that have prognostic significance such as kidney function (health professional)."* *—"Yeah, obviously that one is a harder concept to get the head around. It involves understanding the risk of how your kidney health interacts with other aspects of health. And that's a harder concept sometimes, but yeah, I think that's a good one. I mean, obviously, CKD is a very comorbid condition (patient)."*
Preventing disease progression	*—"There is a lot of ignorance about how kidney function should be evaluated and how to avoid the progression of the disease (health professional)."* *—"Oh, we're all going to die, but what can I do to prevent it? Or how can I have a better life? (patient)."* *—"We know that if our kidneys aren't functioning properly, we're going down the slippery path, so that is our focus, or it's my focus. If I get a lower function, I'm deeply concerned. If I've had a blood test and find my kidneys aren't functioning as well, that freaks me out. Any change in blood analysis freaks me out because to me, it's symbolic that the problems are getting worse (patient)."* *—I think a lot of our patients do value it because once they get the grasp, the concept as was saying, about a sort of percentage kidney function, it's a relatively easy way of them understanding whether they're getting worse or staying the same. So, it's a relatively easy handle on how their disease is doing. And also, a lot of them live in fear of dialysis and see dialysis as almost worse than death (health professional)."* *—"Doctors were concerned about death and hospitalization, when I saw that, it felt a little bit like it was based on their world, what they live with and what they deal with as opposed to... Death, I just think if I can do everything I can to look after myself, it's going to happen at some point, but I just delay it (patient)."*
Living a fulfilling life	*—"It's just getting enjoyment out of life. What is it, that you need to feel whole, right? (patient)."* *—"The constant, what if, what if, what if, and that is how I feel that it impacts upon life's participation from a patient perspective (patient)."* *—"Because for many people in that part of the world [Africa], CKD, whatever treatments they get, they have to pay for themselves. And when they realize that there is something so monumental facing them, then they begin to wonder, "Okay, how soon am I going to die? Am I going to be able to provide for my family? (Health professional)."*

	—"For me, it's just getting enjoyment out of life. What is it that you need to feel whole, right? Because we don't feel whole anymore because we know there's something wrong. So, how do we get that back? (patient)."
Protecting mental health	*— "There has definitely been a psychological effect of having kidney disease, and that has obviously had an effect on me (patient)."* *—"Maybe I would have been a happier person if I didn't have kidney disease (patient)."* *— "One of the things that came to my mind was sort of that holistic approach to the disease and yes, where it's specifically mentioning here your kidney function and your cardiovascular disease. But I also look at it from how it's affecting me emotionally, how it's affecting me mentally and things like that, too. And I find that there's such an opportunity to take care of those aspects of your health, whether it's something your team is looking at, or whether it's something that you are looking for solutions yourself. I think there's a real balance there that's important. And that's part of the Indigenous way of knowing, too, is having that balance of everything because if one thing is out of balance, everything is out of balance (patient)."* *— "You withdraw from your social group, you withdraw from your educational part, you withdraw from participation. It's hard to address whether it's a mental issue or physical issue (patient)."* *—"I also think motivation and that link with depression that, actually, when you can't do things, you can slip into a very slippery cycle of depression and not wanting to do things. I think, if you felt a bit better, maybe you'd want a bit more life participation, but that slips away(patient)."*
Facilitating patient empowerment in their own care	
Raising awareness and improving knowledge	*—"I don't know what my kidney function is unless my nephrologist tells me (patient)."* *— "I want to know what my diagnosis is, then what my treatment is, then what my prognosis is with treatment and my prognosis without treatment (patient)."* *— "When a patient doesn't want to control their blood pressure, I always tell them it's okay, and this is important because if they have a cerebrovascular accident, their quality of life and what they will be able to do in life will be very different (patient)."* *—"Honestly, I don't think about this. They talk about blood pressure a bit. ...They just give you the magic little BP, heart drugs because the kidney affects the blood pressure, et cetera, but they never really say, "Oh, by the way, this is going to be one that's going to affect your life later on (patient)."* *—" I think what strikes me about the cardiovascular disease, and again, this is from my own perspective, but I think a lot of people don't know the impact of that (patient)."* *—"Working with people with diabetes, then we tried to discuss with people with early kidney disease and diabetes with slight proteinuria, but otherwise normal kidney function and make them interested in kidney disease. They had no interest in kidney disease (patient)."* *—"But my problem was, I had never realized that these things were down to the CKD, I have other issues. So, I just thought it was my life, the age I'm getting to, and all the other issues. Whereas seeing this, I'm seeing that a lot of these things are affected by the kidney disease, which I'd never thought of before (patient)."*
Tracking and self-monitoring health status	*— "I have learned to eat healthy and be rigorous, I spent two years with a psychiatrist and that helped me to be rigorous with the medication, I take about 16 pills a day of different medications, and I am not depressed about doing. it is part of my life, and I take it that way. It is to be orderly to have better health (patient)."* *—"My life changed because of the diagnosis, actually, and I tried not to change anything, but the matter of food changed and what impacted me the*

	most, because I had a different diet before and now, yes I have a piece of meat with salad (patient)."
	—"You go and see your nephrologist, and they're just really into kidney function.... But in terms of getting attention for caring for my potential cardiovascular disease, or the fact that the cysts on my liver are causing me problems what I eat now, that's kind of not dealt with (patient)."
	—"I think a lot of those other symptoms that maybe patients have rated higher, like fatigue, and edema, and depression, and anxiety, those are... I mean, I think with many chronic diseases, those are sort of these... They're not soft symptoms. I mean, I feel them acutely, but from a clinical perspective, they often are (patient)."
	—"I think a lot of our patients do value it because once they get the grasp, the concept as Ike was saying, about a sort of percentage kidney function, it's a relatively easy way of them understanding whether they're getting worse or staying the same. So, it's a relatively easy handle on how their disease is doing (patient)."
	—"In some senses it would be good for these core outcomes to not potentially just be used in clinical trials, but also to shape things that are important routinely in clinical care (health professional)".
	—"If it becomes an important measurable objective of patients, it can be something that can be incorporated into routine care. It can be asked when patients come to clinic (patient)."
	—"A lot of our patients do value it because once they get the grasp, the concept as Ike was saying, about a sort of percentage kidney function, it's a relatively easy way of them understanding whether they're getting worse or staying the same (health professional)."
Maximizing autonomy and modifying lifestyle	*— "The renal patient is autonomous and a fighter, he seeks all the means to be able to achieve and try to make a life if not 100% normal (patient)."*
	— "Try to make the most of the days, try to be autonomous and not depend on other people or caregivers. Thank God I didn't have to go through that stage (patient)."
	—I kind of just think I will look after myself the best I can and slow down the progression of the disease by managing it as best I can to minimize when that happens. But I see it as something that's going to change in my life, that I'm going to have to deal with, and I'm going to have to get on with (patient)."
Ensuring applicability to broad geographic areas and populations	
Implementable in different resource settings	*—"I think the answer to this question will be very different depending on the culture and the part of the world you come from (patient)."*
	—"For many people in that part of the world, CKD, whatever treatments they get, they have to pay for themselves. And when they realize that there is something so monumental facing them, then they begin to wonder, "Okay, how soon am I going to die? Am I going to be able to provide for my family?" (patient)."
	—"It all depends on the monetary value. I think all four outcomes are determined by one cause or one root cause, which is how much I can afford and how can I get in that facility, or treated? (patient)."
	—"A number of these are already well reported. Kidney function, I believe they are often reported. Cardiovascular disease, like Vivek said earlier, is quite nebulous in many areas, but I guess something like maybe blood pressure measurement would be reported or occurrence of stroke or myocardial infarction and all of that. Death is always an outcome we nephrologist we are interested in, especially for prospective studies, long term and all of that. So, I think those ones, they are really well reported (health professional)."
Relevant to all types and stages	*—"When CKD people get to end-stage kidney disease, lot of them don't live long because they can't afford dialysis for a long time (patient)."*

of chronic kidney disease	—" *Obviously, CKD is a very comorbid condition. Most people have more than one condition, and therefore it's hard to nail outcome measures that are really relevant across the board to everyone. But I think those four are pretty good, actually (health professional)."* —*"From my perspective, it's absolutely spot on. I mean, those are my major concerns (patient)."* —*"The medicine that you're on between stages one and five, what are they, and are they going to affect my ability to be able to carry on doing what I was doing before? (patient)."* —*" I just wanted a bit of a reality check here and just to remind ourselves that the majority of people who have chronic kidney disease actually don't get to dialysis, don't need a transplant, but it does potentially impact on their lives. So, I think we have to remember that we are writing this for the whole population of people with chronic kidney disease (patient)."*
Feasibility for implementation	
Standardizing definitions and measures	— *"For some patients probably life participation involves whether they are able to carry out social activities as before, their employment, their sleep, their energy and their interests (caregiver)."* —*"Life participation definitely needs a new measure (patient)."* — *"Maybe the way to measure life participation have to be different dimensions (patient)."* —*"Many people would not really understand the concept of kidney function (health professional)."* —*"There is a lot of ignorance about how kidney function should be evaluated and how structural damage can be identified that is sometimes not associated with functional impairment and how to avoid the progression of the disease, obviously as it is had deteriorated this is going to impact the activities of daily life (health professional)."* —*"The concept of life participation, because to me that is a qualitative outcome, and we know that qualitative outcomes are extremely difficult to quantify. So that means that becomes sort of a fluffy concept. And we have to be very careful what we do with that. Do we want to have some very specific ways of measuring and interpreting life participation, thereby quantifying the qualitative outcome that is life participation? I think that's worth a discussion (health professional)."* —*"They've got to do this in a way which is easy to do, easy for participants to actually provide information, easy for trialists to collect it and record it (patient)."* —*"Especially for shorter term trials, well, in all trials, you have to consider how long the follow-up is as to therefore what an appropriate outcome measure is...the trials are neither big enough, nor long enough to capture actual cardiovascular events. So, I think we could do with some standardization on what's a good surrogate for cardiovascular health in CKD that's practical and easy to measure and fairly inexpensive and can be done without too much expensive and specialist equipment (health professional)."* —*"We tend to just lump the cardiovascular disease as one entity, but in fact, with cardiovascular disease, there are different types of cardiovascular disease. The impact is also very different to the patients. And perhaps I felt that maybe we should more fine-tuned what we meant by cardiovascular disease rather than just lumping everything into this category (health professional)."* —*"Life participation, like we've all mentioned, it means completely different things to people. I think it will also be related to the stage of CKD. And I guess it's a progressive thing. So someone with stage one CKD, life participation will not even be coming in on the horizon for that person because you are able to do everything. You're not really thinking about that. It depends on where the person is situated. But I guess as CKD continues to progress, obviously we*

	are talking CKD pre-dialysis, then different things begin to literally arise from the horizon for that person (health professional)." *—"Maybe we can think about stratifying that into different dimensions in measuring your life participation because, to the patient, probably that involves whether they are able carry out social activities as before, their employment, their sleep, their energy and their interests. So maybe the way to measure it have to be different dimensions (health professional)."* *—"We have all these definitions of cardiovascular disease, it's so heterogeneous that we need to standardize it so much better (health professional)."* *—"Life participation and cardiovascular disease, I guess those are the two areas we really need to define: what component of life participation? Because if we make a list of life participation from here to the end of the world for different people, which one of those will be the ones that are really key, good for patients and for nephrologists all across the world, that should be included as an outcome? (Health professional)."* *—"What kinds of tools, there's things like the SF-12, which measures sort of health-related quality of life, and the question is, are they good enough or do we really need something else? So that to me is, will the standard scales really be the thing that people need? (patient)".* *—"My only issue with these is that how were they really defined. Cardiovascular is incredibly broad. And I suspect the patients might meant heart attack or stroke, but actually it's much broader than that. So, if you wanted to capture things in a trial, you might need to be a bit more specific because there are a lot of questions you need to ask to establish if someone's got cardiovascular disease, to get the whole range (patient)".* *—"The first one is how to quantify kidney function. There are so many variables. Decline in glomerular filtration rate is maybe the most important also for patients of 30, 40, 50%. The hard outcome is dialysis (patient)".* *—"We need to define the terms and we need to have instruments that do a good job of actually measuring the concepts of what we're trying to measure (patient)".*
Fostering patient participation and involvement in trials	*—"I think there is a strong movement towards patient-centered outcome design and clinical trials. So, I think if there is a greater awareness in the publications about these fundamental results and the acceptance of industry regulators (patient)."* *—"I think from a regulatory buy-in perspective and also industry buy-in, I think there's strong movement towards designing patient-centric outcomes and clinical trials. So, I think if there is greater awareness in publications about these core outcomes and buy-in from regulators in industry, I think this will be certainly adopted pretty quickly because of strong drive towards representing the patient voice in clinical trials(patient)".*
Engaging triallists, industry and regulators	*—"These results from the perspective of CKD study planning resonate very strongly with clinical development in the industry (health professional)."* *— "These are four outcomes that we focus on when we present these studies to authorities in terms of how we present the data (health professional)."* *—"they've got to do this in a way which is easy to do, easy for participants to actually provide information, easy for trialists to collect it and record it (health professional)."* *—"People who actually design the studies need to be around the table when this is being developed (health professional)."* *—"As a clinical trialist, answering the questions that my patients want, make it easier to recruit. So, it's more likely that a patient's going to say, yes, to join a trial if I say to them well, we're investigating fatigue, or your life participation than a blood test that may mean very little to you (patient)".*

	—"Life participation is where either it's rudimentary, simple, not very meaningful, but it needs to be pushed. It needs to be pushed to be included in trials (health professional)". *—"I think from a regulatory buy-in perspective and also industry buy-in, I think there's strong movement towards designing patient-centric outcomes and clinical trials. So, I think if there is greater awareness in publications about these core outcomes and buy-in from regulators in industry, I think this will be certainly adopted pretty quickly because of strong drive towards representing the patient voice in clinical trials (health professional)".* *—"I've got three things in terms of how they can be implemented. One is awareness that they exist; the core outcomes exist. The second is that the messaging is aimed at those that make the decisions in clinical trials, either in funding or design. So, who has the power in that relationship? And then finally, I'm not sure we stress enough the benefits of using them both for research, but also clinically and from a patient perspective. And if we can't tell people why it's so good to use them, they won't bother using them (health professional)".* *—"I mean, these from a planning CKD trials perspective, these resonate very strongly with clinical development in the industry. These are four outcomes that we focus on when we present these studies to the regulatory authorities in terms of how we present the data (health professional)".*

Table 5.2 Recommendations for establishing and implementing core outcome domains for trials in adults with CKD

Core outcome domains for trials in adults with CKD should:
• Capture major life-threatening outcomes (e.g. death, cardiovascular disease) • Capture the ability to participate in meaningful activities of life activities • Enable patients to monitor disease progression • Support self-management • Be relevant across diverse populations and settings
Implementation of core outcomes may be facilitated by:
• Identifying and/or developing simple, meaningful, and validated measures that can be feasibly implemented in trials, including across different resources settings • Supporting a patient-centered culture to include patient-reported outcomes • Engagement of key stakeholders including triallists, industry and regulators

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Chapter 6: The impact of chronic kidney disease on life participation: a workshop with patients, caregivers and health professionals in Latin America

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This chapter is structured as per the journal article.

6.1 Abstract

Background: Patients with chronic kidney disease (CKD) carry symptom and treatment burden, which together with co-morbidities, can impair their ability to engage in life activities. Different values and priorities regarding life participation may vary depending on the population and setting. We aimed to describe the perspectives of life participation in patients with CKD not requiring kidney replacement therapy in Latin America.

Methods: In April 2024, a workshop (with facilitated breakout groups) was held with patients, caregivers, and health professionals in Spanish language to discuss the impact of CKD on life participation in patients with CKD. Transcripts were analysed thematically.

Results: 66 participants, including 51 patients and caregivers, and 15 health professionals from five countries (Argentina, Chile, Uruguay, Bolivia and Peru) attended. Four themes were identified: despair and sense of doom (coming to a sudden halt, diminished involvement in social activities with family and friends, paralyzing fear, fragility and vulnerability, losing mental fortitude); stigmatized, and judged (alone in the diagnosis, reprimanded for dietary choices, discriminated by employers and colleagues); debilitating symptoms (incapacitated by pain, fatigue impairing functioning); threatening life goals (obscuring decision-making around family planning, relinquishing career aspirations); and garnering hope and strengthening resilience (overcoming challenges with family support, finding strength in spirituality, encouraged by clinicians, physical activity to promote well-being).

Conclusion: Patients with CKD experienced despair, hopelessness, loneliness and isolation, debilitating symptoms, and uncertainty about their family and vocational goals, which contributed to impaired life participation. Strategies are needed to address these challenges to enhance the capacity of patients to live well with CKD.

6.2 Introduction

Patients with chronic kidney disease (CKD) have an increased risk of mortality, life-threatening co-morbidities including cardiovascular disease, and experience treatment complications and side-effects[1]. Patients with CKD may experience increasing symptom burden as the disease progresses, which can be debilitating and impair their overall quality of life[2]. They may also feel uncertain and anxious about the potential need to need to make a decision on supportive care or kidney replacement therapy including kidney transplant or dialysis[3] .

Life participation, defined as the "ability to participate in activities (e.g. leisure, family, work/study) that are meaningful and important to patients" has been identified as a critically important outcome based on consensus which involved 1,399 participants from 73 countries patients with CKD, their caregivers and clinicians through the Standardised Outcomes in Nephrology (SONG) initiative[4]. Whilst the domains of life participation are broad and applicable to all settings, in certain settings such as Latin America, there may be different values and priorities placed on these domains. For example, there may be specific socio-cultural norms, relating to for example, spirituality, larger family structures, social hierarchy, and an importance placed on self-respective and dignity[5], so that the value placed by patients on different aspects of life participation may have more specific meaning in this population.

Little is known about the perspectives of patients and caregivers on life participation in CKD in Latin America. The aim of this study was to describe the perspectives of patients with CKD, their caregivers and clinicians on life participation in CKD prior to the need for supportive care or kidney replacement therapy. This may inform strategies and interventions to improve life participation in CKD.

6.3 Methods

Context and scope

As part of the SONG-CKD Life Participation initiative, a workshop, conducted in Spanish language, was held in person on the 13th April 2024 in Buenos Aires, Argentina during the World Congress of Nephrology. This workshop report focusses on the perspectives of patients, caregivers, and health professionals on the meaning of life participation, and the challenges and enablers of life participation in patients with CKD (stages 1-5, prior to the need for kidney replacement therapy).

Attendees and contributors

We invited patients with any stage of CKD, including patients receiving kidney replacement therapy (KRT), as they could reflect on their experience prior to receiving KRT. Patients aged 18 years or older were eligible and their caregivers. Health professionals with expertise or interest in CKD, (nephrologists, researchers, allied health, regulators and funders) to attend the workshop. Patients, caregivers and health professionals were invited from CKD patients' network, and societies (e.g. Fundación the Pro Renal Health Foundation of the Chilean Society of Nephrology, International Society of Nephrology (ISN) and Sociedad Latino Americana de Nefrología e Hipertensión).

A total of 66 participants from five countries participated. The 51 patients and caregivers were from Argentina (n=41), Chile (n=9) and Uruguay (n=1). The 15 health professionals (nephrologists, researchers and allied health professionals) were from five countries,

including Argentina (n=6), Chile (n=5), Uruguay (n=1), Bolivia (n=1) and Peru (n=1). The full list of attendees of the life participation workshop is provided in Supplementary File 1.

Data collection

Prior to the workshop, the workshop program and background materials were shared with all attendees. The workshop question guide was developed based on the literature and input from patients, caregivers and health professionals, and focussed on the impact of CKD on life participation (Supplementary File 2).

Participants were allocated to breakout groups comprised of seven to ten participants, including both patients, caregivers and health professionals to discuss the topics of the meaning of life participation, and the challenges and enablers of life participation in people with CKD. We sought to ensure that each breakout group included at least two patients/caregivers, and that clinicians were not in the same group as patients under their care. The groups were moderated by a trained facilitator and co-facilitator(s).

After the breakout discussion, all attendees reconvened in a plenary session and each group provided a brief summary of their breakout group discussion, providing a final summary and closing remarks. All discussions were audio-recorded and transcribed verbatim in Spanish language.

Data analysis

The transcripts were entered into HyperRESEARCH software for coding and analysis. Author AMG read the transcripts line-by-line to inductively identify concepts and develop themes and subthemes. The analysis was reviewed by the facilitators to ensure that it captured the full breadth and depth of data. We used investigator triangulation and member checking to ensure that the themes reflected the breadth and depth of the data. The preliminary findings were circulated to all attendees who were invited to provide feedback and additional comments, which were integrated into the final report.

6.4 Results

We identified four themes on the impact of CKD on life participation in patients: despair and sense of doom, stigmatized and judged, debilitating symptoms, threatening life goals, garnering hope and strengthening resilience. The themes and subthemes are described below and illustrative quotes supporting each subtheme are provided in Table 1. A thematic schema depicting the themes is provided in Figure 1.

Despair and sense of doom

Coming to a sudden halt*:* Patients and their families described the diagnosis of CKD as being *"a big shock (caregiver)"* which impeded them from carrying out activities they valued such as going out to birthday celebrations and family gatherings. They felt that everything in life was put on hold —*"I wasn't really living; I was on pause (patient)."* Accepting CKD was psychologically difficult because of the potential of the diagnosis to undermine their ability to live well —*"One wants to continue living, but I can't because of this illness (CKD), and I refuse to accept that (patient)".*

Diminished involvement in social activities with family and friends: Patients felt that CKD prevented them from being able to lead a fulfilling life — *"The first thing I told the doctor was, "This is not life (patient)."* Patients felt their identity and existence were somehow diminished because CKD interfered with their ability to participate in family and social activities — *"How would you feel if you were forced to choose between receiving treatment [CKD medication and diet] and spending time and enjoying with your grandchildren, children, and cousins? (patient)."*

Paralyzing fear, fragility and vulnerability: Patients reported having a heightened sense of vulnerability and were concerned about the seriousness of CKD, which limited their capacity to do activities – *"The fear of being unwell is debilitating and affects my ability to engage in daily activities (patient)."* Some patients became more cautious and refrained from performing daily activities because of weakness; his was also observed by health professionals—*"the patient lost the ability to move and lost significant muscle strength after progressing through stages four and five [of CKD] (health professional)."* Also, clinicians commented, —*" there is a experiencing mental fragility that can hinder the patient's motivation to participate in life, as well as a physical fragility imposed by CKD that prevents the patient from participating, even if he/she desires to do so (health professional)."*

Losing mental fortitude: For patients, it was difficult to remain positive. Some felt "angry with everything," experienced low mood and lost motivation to engage in life participation – *"My mood suddenly did not let me do some activities (patient)"*. The diagnosis of CKD was distressing for patients, which they felt could lead to depression and further incapacitated

them to be able to live life as they wanted —*" If you are experiencing depression, you may find it difficult to carry out daily activities (patient)."*

Stigmatized and judged

Alone in the diagnosis: Some patients felt lonely, socially isolated and lacking in support— *"The diagnosis of the disease led me to distance myself from society. I didn't speak to anyone; I only had conversations with my small group (patient)"*. They were upset about comments received from others that made them feel even more alone in their experience of CKD – "*[They said] I'm sorry to say this, but the illness isn't mine; it's yours(patient)."* Patients perceived themselves as being *"marginalized and different from others"* and felt no sense of belonging in social groups and unable to relate to others in the community.

Reprimanded for dietary choices: Patients at times felt judged and criticized by others for their dietary choices and were exasperated when *"people tell me I can't eat certain foods …it bothers me that I'm drinking juice, and they say, oh, you can't drink that (patient)."* Some avoided social situations as they did not want to be reprimanded about their diet — *"That's why sometimes I try not to go or say every place I go because it bothers me (patient)"*. Caregivers also noted that patients were frustrated having to manage dietary restrictions in social settings — *"For instance, when my son has a meeting with friends, he has to eat differently. This change has caused him frustration."*

Discriminated by employers and colleagues: Some patients felt that employers and colleagues did not have knowledge or understanding about CKD – *"at work, people didn't understand my condition (patient)."* They believed they were prevented from working because of

discrimination by their employer, supervisors and colleagues who assumed they would not be able to work because of CKD —*"I was performing well in a job with sales goals when my boss, despite my performance, told me to go home due to my disease (patient)."*

Debilitating symptoms

Incapacitated by pain: Patients experienced debilitating pain undermined their ability to participate in and activities – *"I couldn't do gymnastics because I lived with cramps, and I couldn't do a lot of activities of daily living."* Caregivers also remarked on—- "*the debilitating symptoms of the disease"* and felt they needed to support patients so they would not succumb to symptoms such as pain*."* Some patients explained that they had to accept and adapt to pain as part of daily life – *"you learn to live with pain; you carry it, and you have no choice (patient)."*

Fatigue impairing functioning: Some patients described the fatigue they experienced as an "unrelenting feeling of exhaustion" that made tasks such as household chores (e.g. cleaning), playing sports, and going for a walk impossible —*" I wanted to go for a walk and couldn't even get up"*. Some stated that the fatigue impaired their ability to function on certain days, particularly if they had already *"spent a lot of energy" during the day before – "I would feel like I am not able to do anything (patient)".*

Threatening life goals

Obscuring decision-making around family planning: For patients, CKD threatened and complicated their decisions regarding family planning —*" I decided not to have children*

because I had to choose between them and my kidney". Having to trade off the risks of adverse pregnancy outcomes due to CKD with wanting to pursue pregnancy was challenging for patients; some reported that clinicians advised them against having children —*" When we were prohibited from having children, it was devastating. It led to a year of therapy for my husband and me. Accepting this took years, and it still hurts."* Similarly, health professionals were aware of the profound grief patients experienced because of this — *"as doctors, asking patients to choose between their illness and pregnancy, it has significant repercussions for them (health professional)."*

Relinquishing career aspirations: Some patients felt that CKD undermined their ability to achieve their career-related goals, and prevented them from advancing in their careers, to get a promotion, and to earn more money. Some patients had to leave their jobs, and it was particularly distressing for those who enjoyed their work —*"I am a special education teacher, working from eight to five in the afternoon. I couldn't do my job well because everything affected me. I had to give up my regular job. It was a difficult decision because it was the career I loved (patient)."*

Garnering hope and strengthening resilience

Overcoming challenges with social support: Patients emphasized that support from family and friends helped them to be able to participate in activities of daily life – "*the support I receive from my family and friends enables me to carry out my daily tasks (patient)."* Encouragement and assistance from family provided patients with the strength to navigate challenges and pursue their interest —*"our support enables our daughter to manage her responsibilities and assist others facing similar challenges (caregiver)."*

Finding strength in spirituality: Some patients turned to faith and religion, and this helped them maintain hope and continue with their daily activities —*" I was never depressed; I never lost the faith that lifted my spirits allowing me to function every day… getting closer to God strengthened me to do my mindful activities every day (patient)".*

Encouraged by clinicians: Some patients felt encouraged by their nephrologist to manage their condition with optimism so they could continue to participate in life activities —*"The support from my doctor was essential; it energized me to approach the treatment differently to be able to do my activities of daily living.*" Health professionals also recognized that providing care should extend beyond the medical focus, and to — *"understand how our patients feel and how they can participate in meaningful activities. This is just as important as monitoring their creatinine and ferritin levels.* However, some health professionals acknowledged that they may not have adequate time in clinical consultations to assess and address life participation —*"Unfortunately, we are limited to fifteen minutes for consultations. We must evaluate our patients' life participation shortly and easily if we are going to do that."*

Physical activity to promote well-being: Patients emphasized that engaging in regular physical activity helped to improve life participation —*"Doctors, in addition to giving patients prescriptions for medications, they should suggest playing sports to stay physically active (patient)."* Physical activity improves their energy and well-being enabling them to engage in daily life activities *"exercise develops a lot of hormones that ultimately encourage you and provide you with energy to do things (patient)."*

6.5 Discussion

Patients with CKD felt hopeless which hindered their motivation to engage in activities they enjoyed and found fulfilling including socializing with family and friends. Some patients felt that their life was on hold and were anxious because of the uncertainty CKD progression and potential need for kidney replacement therapy. Judgement and misunderstanding from others, including about their dietary restrictions, exacerbated their sense of loneliness, and made them reluctant to participate in social activities. Symptoms including pain and fatigue were described as debilitating and undermined their daily functioning. Pursuing life goals, particularly regarding starting a family and work or career aspirations were jeopardised because of CKD, which was profoundly distressing and disappointing for patients. Some depended on family and spiritual support to continue in their daily activities and appreciated encouragement and help from clinicians to manage their treatment so as to minimize the disruption and limitation it had on their daily living.

The findings of the workshop reflect the challenges identified by other patients with CKD, including the inability to maintain work and study, feeling depleted and being unable to socialize, and having to reorient goals and plans in terms of their career and family planning because of the uncertainties related to their health[6, 7]. Of note, the workshop participants appeared to emphasize the centrality of being able to participate in family activities as this was inextricably linked to their identify and quality of their existence, and the consequences of dietary restrictions on hindering their mood and motivation to engage in social activities. This reflects the Latino culture, whereby a high value is placed on family and food[8]. For Latinos, loyalty to the extended family precedes individual needs, and that may intensify the impact of CKD on patients' social roles and well-being, this concept is known as "familismo[9,

[10]." Latino patients with diabetes have also reported feeling social pressures within their family and community to consume traditional foods which are high in fat and calories[11, 12]. This reflects the Latino cultural value of "simpatía" which refers to respecting the wishes of others to maintain good interpersonal relationships, which explains why patients may feel that declining food at a social gathering is considered impolite and unacceptable[13, 14].

For patients, support and encouragement from family enabled them to engage in life participation. Family support has been reported to be vital for Latino patients in helping to manage and adhere to treatment regimens and lifestyle changes (including diet and exercise) to manage chronic conditions including diabetes[12]. Other studies conducted with patients in Latin America have also reported that family members have a critical role in helping patients to manage their treatment and symptoms[15]. For Latino patients, faith and religion have also often been identified as a source of support that provides strength to cope with their illness, and to face their fears and maintain a positive outlook[16]. Some patients felt encouraged by their nephrologist to manage their condition and treatment with optimism. In the context a patient-provider interaction, "personalismo," a cultural construct that values relationships based on warm, caring, and trusting interactions[17], allows patients to express emotions, seek help, and promote an active-role in between clinician and patients to improve their ability to engage in life activities such as exercise, hobbies, family/friend activities, employment, housework and/or study.

Our workshop involved patients, caregivers and health professionals from multiple countries in Latin America and was conducted and analyzed in Spanish language to ensure the capture cultural and linguistic nuances. Data saturation was achieved as all the concepts were identified in more than one breakout group. We used investigator triangulation and member

checking to ensure that the themes reflected the breadth and depth of the data. However, there are some potential limitations. The transferability of the findings to other populations and settings is uncertain.

There is a need to improve life participation in patients with CKD and strategies that encompass support for mental well-being, social connections (including how to manage dietary restrictions in social settings), vocational rehabilitation, symptom management, and family-based interventions are suggested. We suggest that patients should have access to counselling to manage the psychological consequences of CKD the anxiety related to uncertainties regarding their health. Also, culturally sensitive programs that help patients to engage in social activities, and to address concerns and difficulties with dietary restrictions in social settings may help improve the social aspects of life participation. Such interventions may benefit from the involvement of dietitians, who could assist patients with dealing with social values and pressures relating to their diet[18, 19], and how to create family meal plans that encourage better food choices. Patients may also require assistance in being able to maintain work and this may involve referrals to an occupational therapist and vocational rehabilitation programs addressing workplace problem-solving and advocacy, which have been shown to improve employment outcomes in patients with chronic disease[20, 21]. One study demonstrated that a counselling and education program delivered by social workers and nephrologists improved ability to maintain employment in patients with CKD[22]. Identifying and addressing debilitating symptoms, such as pain and fatigue, is also needed. Physical rehabilitation programmes for adults receiving dialysis have been shown to improve the ability to perform daily activities and physical functioning[23], which may also be beneficial for patients with CKD.

We also suggest the need to assess life participation in patients with CKD in clinical and research contexts. The SONG-Life Participation (SONG-LP) instrument has been developed and has validated as a core patient-reported outcome in English-speaking adults with a kidney transplant[24], and current work is being undertaken to assess its psychometric robustness for use in the CKD and dialysis populations. The instrument addresses the domains of leisure, family, work and social, which reflects those identified in the workshop. We suggest the need for cultural and linguistic validation of the SONG-LP measure so that it can be used in Spanish-speaking populations, and thereby broaden its applicability for implementation in trials, research and other relevant settings.

Patients with CKD in Latin America experience impaired life participation and being unable to engage in social activities with family and their community diminished their sense of wellbeing. Culturally responsive strategies and interventions to help improve life participation in patients with CKD in Latin America may help to enhance their mental and social well-being, and ultimately overall health.

Acknowledgements

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Figure 6.1 Thematic Schema

Table 6.1 Illustrative quotes

Despair and sense of doom	
Coming to a sudden halt	"Accepting the disease is challenging because people want to continue living their lives as before" (patient) "Many patients wake up in bed, unable to engage in any activity, and suddenly find themselves diagnosed as kidney patients without understanding the reason" (patient)
Diminished existence in being isolated from family and friends	"Chronic kidney disease limits your ability to participate in certain activities with others" (patient)
Paralysing fear, fragility and vulnerability	"The fear of not getting sick paralyses you and impedes daily life activities" (patient) "It's part of my life now to carry this disease" (patient) "You feel incapable" (patient)
Losing mental fortitude	"A person's mood can also be influenced by how they cope with their illness" (patient)
Stigmatised and judged	
Alone in the diagnosis	"I faced a social crisis with the rest of the world" (patient) "I became socially isolated as a result of my CKD" (patient) "When we first receive a diagnosis, we often feel alone, and that is what happened to me" (patient) "You stop doing your leisure or family gathering because you are worried about it" (patient)
Reprimanded for dietary choices	"I have to inform everyone that I have CKD and cannot consume alcohol or meat, so please do not pressure me to do so" (patient) "It bothers me when they say, "No, you can't eat that; no, you can't drink that" (patient) "I visit my parents' house, where they prepare a lovely meal. I say, "Mom, this has too much salt! Why didn't you set aside a pot for me? "(patient)
Discriminated by employers and colleagues	"I'm meeting all their goals at work, yet they are discriminating against me based on their ignorance about kidney disease" (patient)
Debilitating symptoms	
Incapacitated by pain	"I was completely knocked out [body pain] physically" (patient)
Fatigue impairing functioning	"He sometimes feels frustrated because he can no longer do domestic tasks he used to manage." (caregiver) "Today, I can do everything, but two years ago when I was sick, it was not like that" (patient) "In a tennis game I ended up lying down because I was passed out and I didn't play anymore" (patient)
Threatening life goals	
Complicating decisions regarding family planning	"My doctor gave me the choice between pregnancy and my kidneys, but I decided against it to prioritize my health." (patient) "The thought of undergoing dialysis while caring for a baby is unimaginable." (patient)
Relinquishing career aspirations	"How can we suggest to doctors that these patients have difficulties studying for a career or finding work? (HP)
Garnering hope and strengthening resilience	
Overcoming challenges with family support	"We travelled, and I was worried the whole time: 'Let's see how my daughter is; let's see how she is.'" (caregiver) "For me, this is crucial to know about life because it helps me support my daughter through this process, understanding that this illness may either improve or worsen" (caregiver)

Finding strength in spirituality	"Being closer to the Church has greatly strengthened me" (patient)
Encouraged by clinicians	"I have a doctor who is a seven, a ten, and a million; I love him" (patient) "The doctor emphasized that finding a treatment to cure your kidney disease while enabling you to lead the best life possible is crucial (patient)
Physical activity to promote well-being	"Practice sports regularly as part of managing kidney disease".(patient) "I believe that doctors, in addition to giving the prescription, must indicate the essential of playing sports to stay physically active" (patient) "Physical activity is essential for me" (patient)

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Chapter 7: Discussion and conclusions

7.1 Summary of findings

The overall aim of my thesis was to establish a core outcomes set to be reported in trials in patients with CKD prior to the need for kidney replacement therapy.

Specifically, this thesis addressed the following objectives:

1. To identify patient and caregiver priorities for outcomes in CKD (Chapter 2)
2. To describe the experiences of nephrologists on caring for patients receiving in-centre haemodialysis during the COVID-19 pandemic in Latin America (Chapter 3)
3. To generate consensus among patients/caregivers and health professionals on critically important outcomes for trials in CKD prior to kidney failure and the need for kidney replacement therapy, and to describe the reasons for their choices (Chapters 4)
4. To establish a consensus-based set of core outcomes for trials in CKD (prior to the need for kidney replacement therapy) (Chapter 5)
5. To describe the perspectives of life participation in patients with CKD not requiring kidney replacement therapy in Latin America (Chapter 6)

In Chapter 2, I described the use of nominal group technique as a mixed methods approach to identify the priorities of patients and caregivers on outcomes of importance in CKD and the reasons for their choices. In Chapter 3, I conducted qualitative semi-structured interviews to describe the range and depth of the perspectives of nephrologists on caring for patients receiving in-centre haemodialysis. In Chapters 4 and 5, I used an international Delphi survey

and multi-stakeholder workshops in English and Spanish languages to generate consensus among patients, caregivers and health professionals on critically important core outcomes to be reported in trials in patients with CKD not yet requiring kidney replacement therapy. Building on this work in which life participation was identified as a core outcome, in Chapter 6, I conducted a stakeholder workshop with patients, caregivers, and healthcare professionals in Spanish language to discuss life participation in patients with CKD net yet require kidney replacement therapy in Latin America.

Patient, caregiver and health professional priorities for outcomes to inform decision-making in CKD

Chapter 2: Identifying outcomes important to patients with CKD and their caregivers

Patients with CKD and caregivers in United States, Australia, and the United Kingdom who participated in focus groups with nominal group techniques identified outcome of importance for trials in CKD. The top ten prioritised outcomes were: kidney function, life participation, mortality, fatigue, end-stage kidney disease (ESKD), blood pressure, anxiety, cognition, depression and sleep. The five themes I identified which reflect the reasons for their priorities included: re-evaluating and reframing life, intensified kidney consciousness, battling unrelenting and debilitating burdens, dreading upheaval and constraints, and taboo and unspoken concerns.

There were some differences in how outcomes were prioritised based on whether they were patients or caregivers, and by country. Patients gave highest priority to kidney function, ESKD, fatigue, mortality and life participation. Caregivers placed a greater emphasis on

mental health and cognitive outcomes. Across all three countries, seven outcomes appeared among the top 10: kidney function, end-stage kidney disease (ESKD), mortality, fatigue, life participation, blood pressure, and cognition. The five outcomes rated highest by participants in the United States were ESKD, kidney function, mortality, fatigue, and life participation; in Australia, they were kidney function, fatigue, life participation, mortality, and cognition; while in the UK, the top five were kidney function, ESKD, mortality, blood pressure, and fatigue.

Kidney function and kidney failure were of top priority for patients with CKD, even above mortality, which reflects their utmost concern about the potential deterioration of kidney function and consequently requiring dialysis or kidney transplant. The focus on kidney function may be because patients may use outcome to monitor and manage their health to try and slow the progression of the disease (i.e. maintain kidney function). Fatigue, life participation and anxiety were patient-reported outcomes that were highly prioritised. Fatigue in patients with CKD is common, may increase in severity as CKD progresses, and can be debilitating such that it impairs daily functioning.[1] Life participation, is defined as the "ability to participate in activities (e.g. leisure, family, work/study) that are meaningful and important to patients", was also regarded by patients with CKD and caregivers to be of high importance. This reflects a focus on patients wanting to live as well as they could with CKD. The high priority given to anxiety appears to relate to the uncertainty of their prognosis and fear of potentially needing dialysis.

Chapter 3: Nephrologists' perspectives on caring for patients receiving haemodialysis during the COVID-19 pandemic

At peak of the COVID-19 pandemic, I was restricted in my ability to progress with some aspects of the SONG-CKD study and thus pivoted my efforts to address some of the challenges in providing care for patients with CKD during the pandemic. From the semi-structured interviews, I conducted with nephrologists on managing patients receiving haemodialysis during the COVID-19 pandemic, I identified themes including: shock and immediate mobilization for preparedness, personal vulnerability, infrastructural susceptibility of dialysis units, helplessness and moral distress and fostering innovative delivery of care.

Chapter 4: Consensus on outcome of critical importance for trials in CKD

I conducted an international online Delphi survey (Chapter 4) to generate consensus among patients, caregivers and health professionals on outcomes of critical importance to be potentially included in the core outcomes set in CKD. The outcomes deemed most important by patients, caregivers, and health professionals included kidney function, the need for dialysis or transplant, life participation, cardiovascular disease, and mortality. The four themes that reflected the reasons for their priorities for outcomes included: imminent threat of a health catastrophe, signifying diminishing capacities, ability to self-manage and cope, and tangible and direct consequences.

Of note, cardiovascular disease emerged as an outcome of critical importance in the Delphi survey but was not in the top 10 outcomes as identified by patients/caregivers in the focus group study (Chapter 2). In the Delphi survey, patients/caregivers upon reviewing respondent scores and comments from health professionals gained an awareness about the increased risk of cardiovascular disease in patients with CKD.

Establishing a core outcomes set for trials in CKD

Chapter 5: Establishing the core outcomes set for CKD a summary of the workshop discussion

I conducted two international online stakeholder workshops, one in English and one in Spanish language. In total, 61 patients and caregivers and 75 health professionals from 18 countries contributed to the workshop. Overall, they supported mortality, kidney function, life participation, and cardiovascular disease to be included in the core outcomes set for trials in CKD not yet requiring kidney replacement therapy. I identified three themes. Reflecting a comprehensive approach to health meant that the core outcomes addressed both key clinical and patient-reported outcomes to broaden the focus of care and decision-making on the patient as a whole person. Facilitating patient empowerment in their own care reflected the need to include outcomes relevant to decision-making and self-management. Ensuring applicability to broad geographic areas and populations captured the view that the core outcomes should be widely applicable to all patients with CKD and across various settings. Themes that addressed the implementation of the SONG-CKD core outcomes set included standardising definitions and measures, fostering patient participation and involvement in trials, and engaging triallists, industry and regulators.

Life participation, a core outcome for patients with CKD

Chapter 6: Perspectives on life participation among patients with CKD, caregivers and health professionals in Latin America.

Life participation was established as a core outcome for trials in patients with CKD. In a workshop I conducted with patients with CKD, caregivers and health professionals, the five themes that reflected the impact of CKD on life participation included: despair and sense of doom, stigmatised and judged, debilitating symptoms, threatening life goals and garnering hope and strengthening resilience. Patients felt despair and hopelessness when diagnosed with CKD and described their life as coming to a sudden halt, having a diminished existence in being isolated from family and friends, being in a state of paralysing fear, fragility and vulnerability, and losing mental fortitude. Patients with CKD felt stigmatised and judged, misunderstood by others particularly in relation to their dietary restrictions, which exacerbated their sense of loneliness, and reported being discriminated against by employers and colleagues. Debilitating symptoms, including pain and fatigue, undermined their daily functioning. The diagnosis of CKD was also seen by patients to jeopardised their goals in life, particularly in terms of having a family and a career. Garnering hope and strengthening resilience through family support, finding strength in spirituality, and being encouraged by clinicians to overcome daily challenges were some of the coping strategies patients with CKD used to manage the challenges and consequences of their condition.

7.2 Strengths and limitations

The strengths and limitations of the studies have been described in the published articles. This section considers the strengths and limitations of the thesis in its entirety.

An overview of the strengths and novel aspects

In developing the core outcomes set for SONG-CKD, I used a systematic, transparent and inclusive approach based on the well-established methodological framework as recommended by the Core Outcome Measures in Effectiveness Trials (COMET) and Outcome Measures in Rheumatology (OMERACT).[2, 3] I followed the 11 minimum standards for establishing core outcome sets in accordance with the Core Outcome Set-STAndards for Development (COS-STAD) checklist, which included: consideration of the setting covered by the core outcomes set, consideration of the details of the health conditions to be covered (i.e. chronic kidney disease not requiring kidney replacement therapy), consideration of the population, consideration of the details of the intervention, involvement of those involved who will do the research who will use the core outcomes set, involvement of health professionals who could identify important outcomes, involvement of patients/caregivers, consideration of the views of health professionals and patients when generating the initial list of outcomes for inclusion in the consensus process, description of the consensus method, specification of the criteria for including/excluding outcomes, and consideration of the language when describing outcomes for different stakeholder groups.[4] Some of the studies were conducted in two languages, English and Spanish. To capture the cultural and linguistic nuances, I collected and analysed the data in the native language of the participants.

As both the coordinator of the SONG-CKD initiative and primary author on all related publications, I have received formal training in consensus methods (nominal group technique, Delphi survey), qualitative research (focus groups, semi-structured interviews), and in conducting stakeholder consensus workshops and a focus group also from my supervisor Professor Allison Jaure.

I also applied best practice approaches for involving patients and caregivers throughout all stages of the SONG-CKD project. Patients/caregivers were involved as members of the SONG-CKD Steering Committee and contributed to the strategic direction, focus, scope and design of the project. They contributed as co-authors on all publications arising from the SONG-CKD study. Patients/caregiver were involved as co-investigators and also as participants in the focus group study,[5] Delphi survey[6], and workshops.[7]

Across the SONG-CKD project, I involved 1139 patients/caregivers and 1253 health professionals from across 75 countries. The multinational involvement is notable considering that only 22% of core outcome set initiatives involved patients from five or more countries[8, 9], and very few involve multiple languages.

A focus group study employing a nominal group technique, an international survey, and a multi-stakeholder workshop were included in my thesis. The qualitative and quantitative methods utilized were complementary. The quantitative aspects enabled the quantification of stakeholder priorities for outcomes and the qualitative methods were used to generate the reasons, attitudes, and values underpinned the preferences of participants. Specifically in the Delphi survey, I used both the GRADE Likert rating scale and the Best-Worst Scale to ascertain the absolute and relative importance of the outcomes.

The qualitative research presented in this thesis collectively addresses the four dimensions of trustworthiness outlined by Lincoln and Guba: credibility (findings were based on the evidence), dependability (the process was auditable), confirmability (the findings and interpretations were linked to the data), and transferability (the findings are relevant to other populations and settings).[10] The credibility of the studies was ensured through the design of

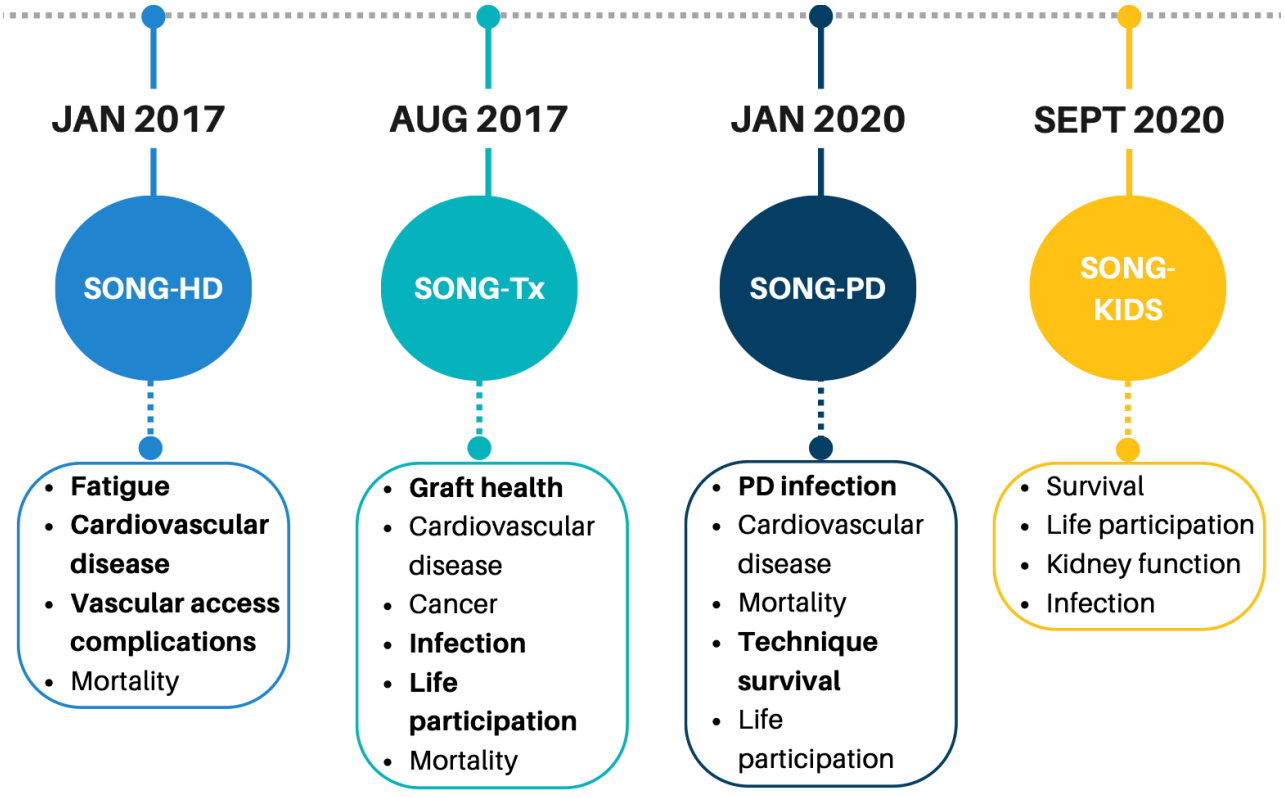
an appropriate question guide, and the use of purposive sampling to include a wide range of demographic and clinical characteristics. The dependability of the studies was demonstrated through the recording and transcription of data, and the use of computer software (HyperRESEARCH) to record all coding decisions. The confirmability of the findings was achieved through member checking of draft findings by participants to ensure that the full range and depth of their views were reflected in the analysis, and the inclusion of raw data in the publications. Transferability of my findings was achieved by providing details about the participants and setting of the studies, and by comparing my findings to other studies conducted in other populations and settings.

This thesis has potential limitations. We acknowledge that the studies were conducted in two languages (English, Spanish) and it was not feasible to include participants from all countries. The studies conducted in person were held in urban locations. Also, some of the studies were conducted online. It is possible that patients/caregivers in rural/remote areas, and those without limited computer literacy or without access to the Internet were precluded from participating. Thus, the transferability of the findings may be limited by these aspects.

7.3 Comparison with other studies

The studies in my thesis were focussed on identifying core outcomes for trials in CKD prior to the need for kidney replacement. In this section, I will discuss SONG-CKD in the broader context of the SONG initiative by comparing the core outcomes with other core outcome sets and compare the findings with other work on the perspectives and preferences of patients regarding outcomes in CKD.

Since 2014, the SONG initiative has established seven core outcomes sets (haemodialysis, kidney transplantations, peritoneal dialysis, children with CKD, polycystic kidney disease, glomerular disease, and CKD prior to the need for kidney replacement therapy) as shown in Figure 7.1. Some of the core outcomes identified for SONG-CKD are common across different streams. Mortality has been established as a core outcome across all SONG core outcome sets. Cardiovascular disease was also identified as a core outcome across all sets except for children with CKD. Kidney function has also been established as a core outcome for children with CKD, polycystic kidney disease, and glomerular disease. Life participation was common across the streams of kidney transplantation, peritoneal dialysis, children with CKD, and glomerular disease.



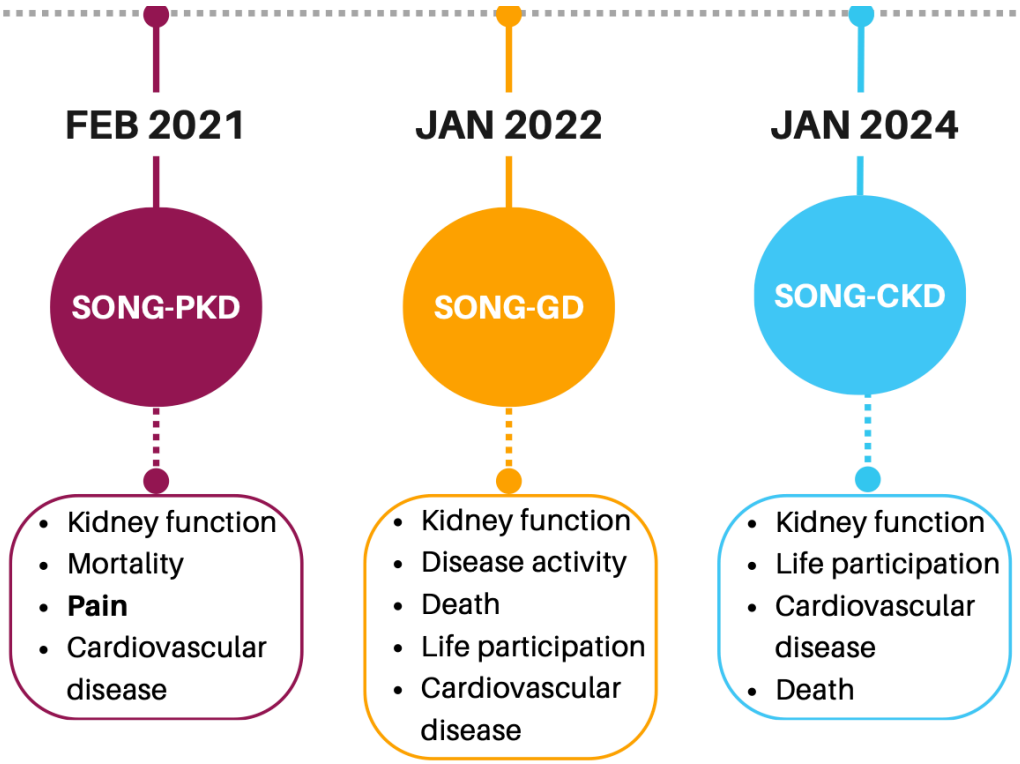


Figure 7.1 Timeline of the development of the SONG core outcome sets adapted from O'Reilly[11]

Other studies have also found that mortality, kidney function and CKD progression, cardiovascular disease, and symptoms (in particular fatigue) are important to patients.[12-16] For patients, kidney function is perceived to be a critical indicator of their kidney health and prognosis and the potential need for commencing kidney replacement therapy, and to support self-management.[5, 17-19]

7.4 Future research

Following on from this work, I will contribute to establishing core outcome measures for each of the core outcomes beginning with life participation. Life participation was the most

important patient-reported outcome identified in SONG-CKD, and is defined as the ability to meaningfully participate in activities of daily living such as work (employment, housework, study), family, social (friends and others) and leisure activities (exercise, hobbies, travel).[20] Despite life participation being a critical outcome for patients and caregivers in CKD, it is inconsistently reported in trials and observational studies, with 41 different measures utilised across 114 studies. Most measures assessed a broader construct (quality of life), including at least one item relevant to life participation, rather than focusing on life participation as a specific construct. The measures varied widely in terms of completion time, response format, number of items, recall period, cost, content, and the availability of psychometric data. Data on the characteristics and psychometric properties of measures of life participation in CKD populations for many of the measures were very limited.[21]

A core outcome measure for life participation (SONG-Life Participation) has been developed and has been initially validated in kidney transplant recipients in English language, and was shown to be content-relevant, internationally consistent and reliable[22]. The SONG-Life Participation instrument is currently being validated in adult patients with CKD and those receiving dialysis. However, the instrument has been developed and validated in English language only. Based on my workshop on life participation, the domains in the SONG-Life Participation appear relevant and meaningful to Spanish-speaking patients with CKD in Latin America. I will commence work to pilot and conduct cultural validation of the SONG-Life Participation Instrument for use as a in Spanish-speaking patients with CKD. The initial phase of this process will involve translation and adaptation in accordance with international guidelines, which includes two direct translations, a synthesised version based on these direct translations, two reverse

translations, and a consensus from an expert committee on a pre-final version, followed by pre-testing with end users and development of a final version (Figure 7.2).[23, 24] I will follow the COSMIN-COMET guidelines for establishing core patient-reported outcome measures.[25] The established measure will undergo validation to evaluate further psychometric properties such as test-retest reliability, convergent/divergent validity, and responsiveness.[25]

Figure 7.2 SONG-LP Instrument, Spanish translation and adaptation[23, 24]

I also plan to design trials of interventions to improve life participation in CKD. Many trials in CKD are focussed on pharmacological interventions and on biochemical outcomes, and

with a particular focus on the Spanish-speaking population in Latin America. Based on research priority-setting initiatives in which patients have identified lifestyle interventions to be of high importance,[26] data from my thesis, and drawing from my own discipline of nutrition and dietetics, I will co-design with patients with CKD a self-management program with a primary focus on diet and evaluate its effectiveness on improving life participation in patients with CKD. The program will also be designed to address the concerns articulated by patients with CKD including how to manage the perceived stigma, judgement and social isolation related to dietary restrictions. This will address critical evidence gap as systematic reviews have demonstrated a lack of high-quality trials of dietary interventions that address outcomes of most importance to patients.[27]

Future work will also involve the evaluation of the uptake of the SONG-CKD core outcomes set in trials. I plan to evaluate the uptake of the core outcomes in published trials and trial protocols, and to assess changed over time.[28] An evaluation of the uptake of core outcomes for rheumatoid arthritis included 273 randomised trials of pharmacological interventions and found that the uptake of core outcomes in trials increased over time.[28] I will apply a similar method to examine the implementation of SONG-CKD core outcomes using trial registries and publications.

7.5 Implications for research, policy and practice

The SONG initiative aims to establish core outcome sets to improve the relevance and consistency of outcomes in trials in nephrology to support decision-making based upon outcomes that are of critical importance to patients, caregivers and health professionals. A strategy for implementing core outcomes has been developed as part of the SONG initiative[29]

and a summary of the ways to support the implementation of core outcomes is provided in Figure 7.3 and outlined in the following section.

Funding agencies

Some funding agencies recommended that applicants consider the use of core outcomes in their submissions. Since 2012, the UK National Institute for Health Research has encouraged applicants applying for funding to conduct trials or evidence synthesis to include core outcome sets.[30]

Regulators

Including core outcomes in regulatory guidance may help to strengthen the uptake of core outcomes. The European Medicine Agency's (EMA) guidance for collaborative clinical assessments recommends that trials should take core outcome sets into account when selecting outcomes.[31, 32] In a broad scientific request to the EMA in 2018, the European Society for Organ Transplantation recommended for the inclusion of life participation as an outcome in trials in kidney transplantation and specifically recommended the use of the SONG-Life Participation Instrument.[33]

Trial registries and networks

Trial registries and organisations can also have a role in facilitating the implementation of core outcomes. The International Standard Randomized Controlled Trial Number (ISRCTN) registry for clinical trials, which is endorsed by the World Health Organization and the

International Committee of Medical Journal Editors, advises trialists to consult the COMET initiative for core outcome sets relevant to the trial.[3]

Reporting guidelines and journals

The SPIRIT Statement, which is a reporting guideline for clinical trials, includes a recommendation to include core outcomes.[34] Encouraging the use of core outcomes in journal authorship policies could facilitate the uptake of core outcomes. As an example, Cochrane Kidney and Transplant has mandated that authors use SONG core outcome sets in Cochrane reviews.

Clinical registries and cohort studies

The inclusion of core outcomes in registries may support the use of core outcomes given that there is growing interest in registry-based trials. Some of the SONG core outcomes have been adopted by the Australian and New Zealand Dialysis and Transplant (ANZDATA) registry.[35]

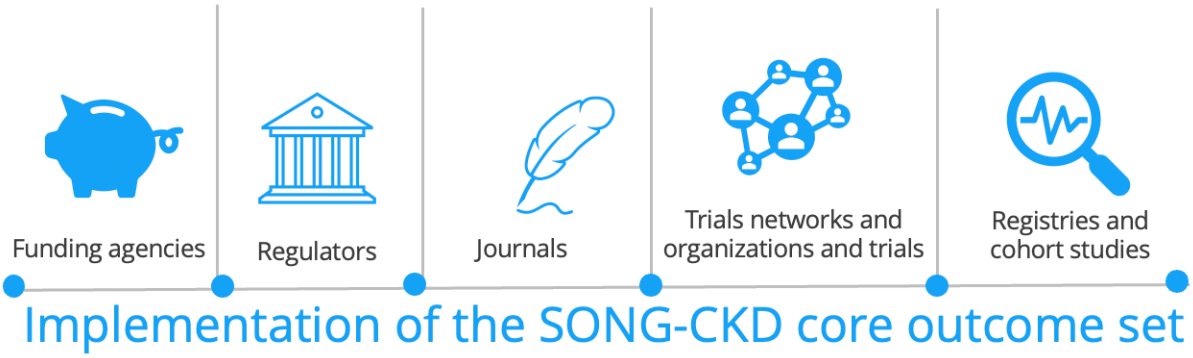


Figure 7.3 Strategies to support the implementation of core outcomes

7.6 Conclusion

The consensus-based core outcomes for trials in CKD include kidney function, life participation, cardiovascular disease, and death. These outcomes were identified by patients, caregivers and health professionals to be of critical importance to be reported in all trials in adults with CKD. Implementing the core outcomes in trials can help to ensure that outcomes of critical importance are consistently reported in trials to improve the evidence based for shared decision-making. Further work is underway to identify or develop core outcome measures. Efforts are also needed to support implementation of the core outcomes in trials and to evaluate uptake over time.

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A.1 Supplementary Table 1. Question guide and list of outcomes

QUESTION GUIDE

1. What happened when you first found out you had kidney disease? Did you have to make any changes in your life (e.g. lifestyle, taking medications, accessing care)? What sorts of decisions did you have to make about your treatment?
2. What were the most important impacts/outcome of chronic kidney disease and treatment (before needing or starting dialysis, or before transplantation) – why?
3. What do you think are the most important to address/report in research in CKD – why? *Facilitator to note down outcomes that were mentioned.* [Outcomes e.g. clinical (ESKD, mortality, CVD), patient-reported (fatigue, life participation, patient activation/empowerment), biochemical (kidney function, blood pressure)].
4. Here is a list of outcomes (impacts of treatment) that have been taking from research in chronic kidney disease, and also research about patient perspectives. Let's go through these and if you have any questions, we can discuss them.
5. What other outcomes would you like to add to this list?
6. Please rank the top 10 most important outcomes, that you think should be reported in research (trials) in people with chronic kidney disease because they are important for decision making. 1 being the most important.
7. [After everyone has completed ranking] Could everyone tell me their top 3? [Write the top three and tally the votes on the board] Does anyone want to explain how they decided on the top 3 outcomes?
8. What are your reactions to these [group scores on the board]? What are some of the reasons for the similar or different rankings?

LIST OF OUTCOMES AND RANKING

What outcomes are important to include in research/clinical trials in early chronic kidney disease (before needing dialysis/kidney transplant)?

Outcome	**Rank**
End-stage kidney disease (need for dialysis/transplant)	
Fatigue	
Kidney function	
Cardiovascular disease	
Life participation	
Blood pressure	
Mortality (or survival, death)	
Hospitalization	
Bone disease	
Anemia (including iron and haemoglobin)	
Infection	
Anxiety	
Depression	

Cognition (or ability to think clearly, remember things)	
Parathyroid hormone	
Pain	

Nausea and vomiting	
Skin (including itch)	
Sleep	
Proteinuria	
Fluid build up / fluid weigh	
Headache	
Sexual function	
Taste	
Diabetes	
Cramps	
Mood*	
Constipation*	
Restless legs*	
Temperature regulation*	
Muscle weakness*	
Fertility*	
Appetite*	
Weight gain*	
Self-esteem*	
Tremor/shaking*	

Outcomes were randomized.

*New outcomes identified by patients/caregivers that were added to the initial list

A.2 Supplementary Table 2. Location and number of participants in each nominal group

Group ID	City	Country	Participants (n = 67)
1	Houston	United States	8
2	Houston	United States	6
3	Dallas	United States	7
4	Armidale	Australia	6
5	Armidale	Australia	7
6	Sydney	Australia	7
7	Sydney	Australia	8
8	London	United Kingdom	8
9	London	United Kingdom	8
10	Sheffield	United Kingdom	2

A.3 Supplementary Table 3. Individual ranking of all outcomes according to commencement of kidney replacement therapy

Not on kidney replacement therapy (n=16)		Commenced kidney replacement therapy (n =38)	
Outcome	**Importance score (95% CI)**	**Outcome**	**Importance score (95% CI)**
Kidney function	**0.41 (0.20, 0.61)**	**Kidney function**	**0.42 (0.30, 0.55)**
Mortality	**0.28 (0.06, 0.50)**	**ESKD**	**0.34 (0.23, 0.44)**
Fatigue	**0.25 (0.14, 0.40)**	**Fatigue**	**0.27 (0.17, 0.38)**
Blood pressure	**0.21 (0.07, 0.38)**	**Mortality**	**0.23 (0.14, 0.33)**
ESKD	**0.19 (0.06, 0.35)**	**Life participation**	**0.22 (0.14, 0.31)**
Cognition	**0.18 (0.04, 0.35)**	**Blood pressure**	**0.16 (0.10, 0.23)**
Life participation	**0.15 (0.08, 0.24)**	**Cognition**	**0.11 (0.05, 0.18)**
Pain	0.14 (0.03, 0.28)	Infection	0.09 (0.04, 0.16)
Infection	**0.12 (0.07.0.17)**	**Cardiovascular disease**	**0.08 (0.04, 0.13)**
Anxiety	0.11 (0.06, 0.16)	Depression	0.08 (0.05, 0,12)

Patients only. Outcomes in bold are included in the top 10 across all groups. ESKD, end-stage kidney disease (requiring kidney replacement therapy)

A.4 Supplementary Table 4. Individual ranking of all outcomes according to country

United States (n=21)		**Australia** (n =28)		**United Kingdom** (n =18)	
Outcome	**Importance score (95% CI)**	**Outcome**	**Importance score (95% CI)**	**Outcome**	**Importance score (95% CI)**
ESKD	**0.39 (0.23, 0.56)**	**Kidney function**	**0.40 (0.27, 0.56)**	**Kidney function**	**0.54 (0.25, 0.73)**
Kidney function	**0.31 (0.19, 0.47)**	**Fatigue**	**0.31 (0.19, 0.44)**	**ESKD**	**0.13 (0.18, 0.47)**
Mortality	**0.24 (0.11, 0.40)**	**Life participation**	**0.30 (0.20, 0.42)**	**Mortality**	**0.31 (0.14, 0.49)**
Fatigue	**0.20 (0.11, 0.30)**	**Mortality**	**0.21 (0.11, 0.34)**	**Blood pressure**	**0.24 (0.11, 0.40)**
Life participation	**0.18 (0.08, 0.31)**	**Cognition**	**0.18 (0.11, 0.27)**	**Fatigue**	**0.24 (0.12, 0.36)**
Cardiovascular disease	0.14 (0.06, 0.26)	**Blood pressure**	**0.17 (0.08, 0.28)**	**Life participation**	**0.19 (0.11, 0.27)**
Blood pressure	**0.11 (0.05, 0.19)**	Anxiety	0.17 (0.10, 0.25)	Infection	0.17 (0.08, 0.29)
Hospitalization	0.11 (0.05, 0.17)	**ESKD**	**0.13 (0.07, 0.21)**	Pain	0.14 (0.04, 0.27)
Infection	0.08 (0.03, 0.14)	Depression	0.13 (0.08, 0.18)	**Cognition**	**0.13 (0.01, 0.29)**
Cognition	**0.07 (0.02, 0.13)**	Sleep	0.11 (0.04, 0.19)	Fluid/weight	0.12 (0.06, 0.18)

Outcomes in bold are included in the top 10 across all groups. ESKD, end-stage kidney disease (requiring kidney replacement therapy)

Appendix B

B.1 Supplementary File 1. COREQ Checklist

No.	Item	Comment	Pages of the manuscript
Domain 1: Research team and reflexivity.			
1	Interview/facilitator	A.M.G	6
2	Credentials	A.M.G (BNtrSc1)	1
3	Occupation	A.M.G, Research Assistant, Dietitian	1
4	Gender	A.M.G (Female)	-
5	Experience and training	A.M.G has conducted and published qualitative research	-
6	Relationship established	2 interviewees were known colleagues	-
7	Participant knowledge of the interviewer	A.M.G is conducting a study to elicit nephrologists' perspectives on providing care to patients receiving dialysis during the COVID-19 pandemic to inform strategies for improving the quality and safety of care for patients receiving dialysis.	-
8	Interviewer characteristics	A.M.G is a PhD Candidate with qualifications in Dietetics and Nutrition	-
Study design			
9	Theoretical framework	Qualitative study (using techniques from grounded theory)	6
10	Sampling	Purposive and snowballing	6
11	Method of approach	Email	6
12	Sample size	N=25 See table 1	23
13	Non-participation	One did not participate because of conflicting schedules.	-
14	Setting of data collection	Zoom	6
15	Presence of non-participants	None	-
16	Description of sample	Refer to Table 1	23
17	Interview guide	Provided in Supplementary File 1	-
18	Repeat interviews	Single interview conducted	-
19	Audio/visual recording	Interviews were audio recorded	6
20	Field notes	A.M.G recorded field notes	6
21	Duration	The mean duration of the interviews was 20 minutes.	-
22	Data saturation	Yes	7
23	Transcripts returned	No	-
Analysis and findings			
24	Number of data coders	4 (A.H., E.L., S.C., A.T.)	7
25	Description of the coding tree	No – see themes	-
26	Derivation of themes	Inductively derived from data	7
27	Software	HyperRESEARCH	7
28	Participant checking	Yes	23
29	Quotations presented	Refer to Table 2	24-25
30	Data and findings consistent	Quotations provided to illustrate each theme.	24-25
31	Clarity of major themes	Yes – themes	7

32	Clarity of minor themes	Yes – see subthemes and description of the themes	7

Appendix B

B.2 Supplementary File 2. Interview guide

Introduction

We are interested in the nephrologists' perspectives on the impact of COVID-19 on the care of patients receiving haemodialysis. We would like to know your opinion about whether you think there are differences in the care of patients on haemodialysis therapy infected by the SARS-CoV-2 virus. What are the first reactions to prepare for the Covid pandemic, the consequences of COVID-19 on the care of patients receiving dialysis, and the expectations and suggestions for post-Covid care?

Part 1: Initial reactions and preparation for Covid-19:

1. When did you initially hear about COVID 19? What was your response to caring for patients on dialysis?
2. What were your main concerns – for patients, for yourself, for the staff?
3. What sorts of things did you have to do to prepare for the COVID-19 in terms of managing dialysis? What were the challenges, and how did you resolve these?

Part 2: Impact of COVID-19 on the care of the patient receiving dialysis

4. What was the most significant impact of COVID-19 on the care of patients receiving dialysis – why? (Access to dialysis, health outcomes, quality of life etc.)
5. Were you able to address these – why, how?
6. What were the biggest challenges for you and the staff, the dialysis unit?
7. What were the most significant changes you have made, and how did you feel about these changes? Did you have patients receiving dialysis who had COVID-19 – what were the biggest challenges for the patient/for you?

Part 3: Expectations and Suggestions for Post-Covid care:

8. What are/what do you expect maybe the challenges or changes patients will face as things improve?

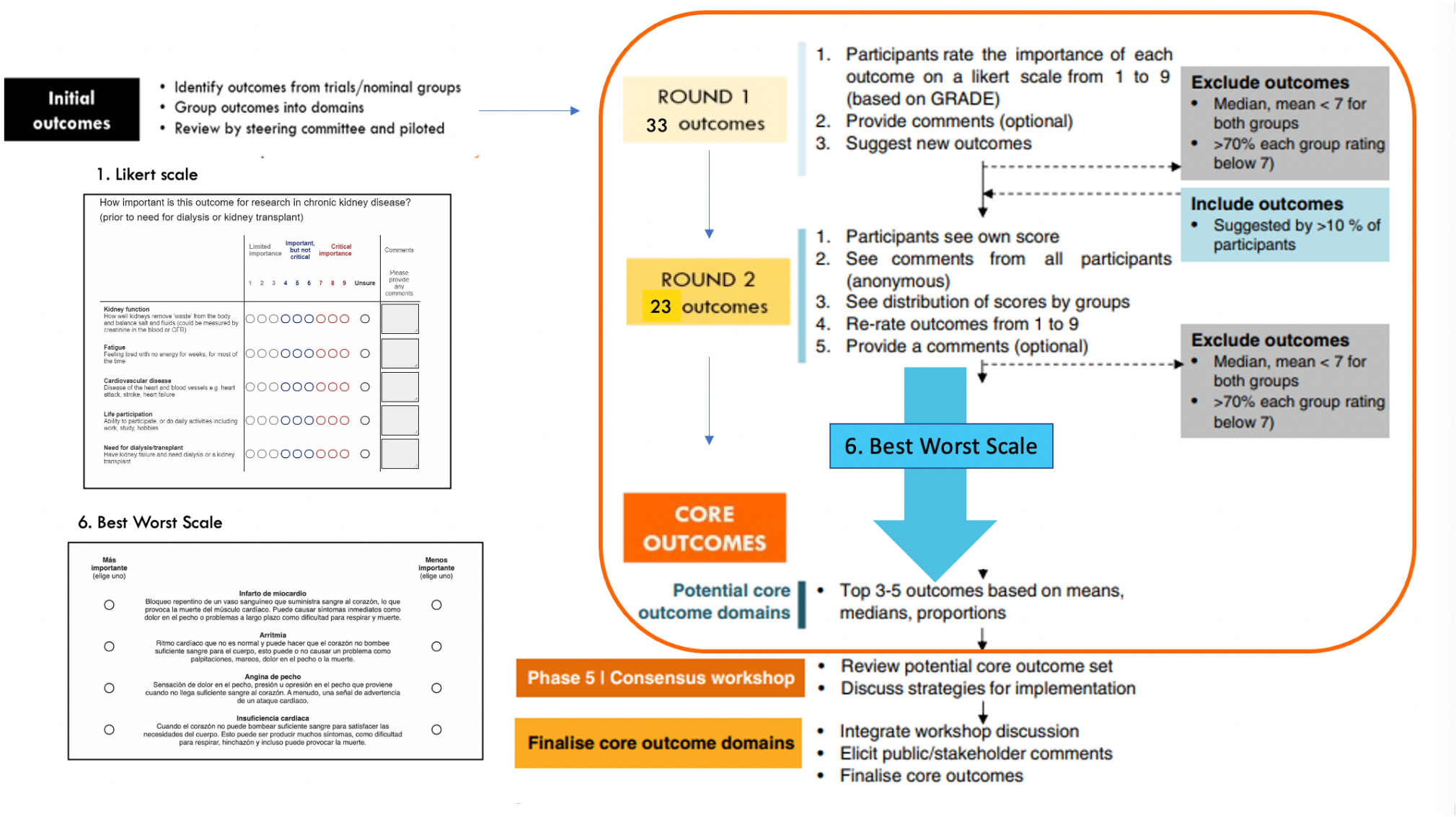
9. What do you expect will happen after COVID-19 with the care of patients receiving dialysis? (Medium to long-term changes?)
10. Are there any changes you should implement or should continue through the post -COVID 19 - why?
11. What are the key learnings you have gained during this pandemic in terms of patient care? Could those apply now and in the future?

Close

Is there anything else you would like to add? Thank you.

Appendix C

C.1 Supplementary Figure S1. Outcome definitions used in the SONG-CKD Delphi survey.



C.2 Supplementary Figure S2: Subgroup analysis of mean Likert scores of patients and caregivers by CKD treatment stage, diabetes, gender, age and country.

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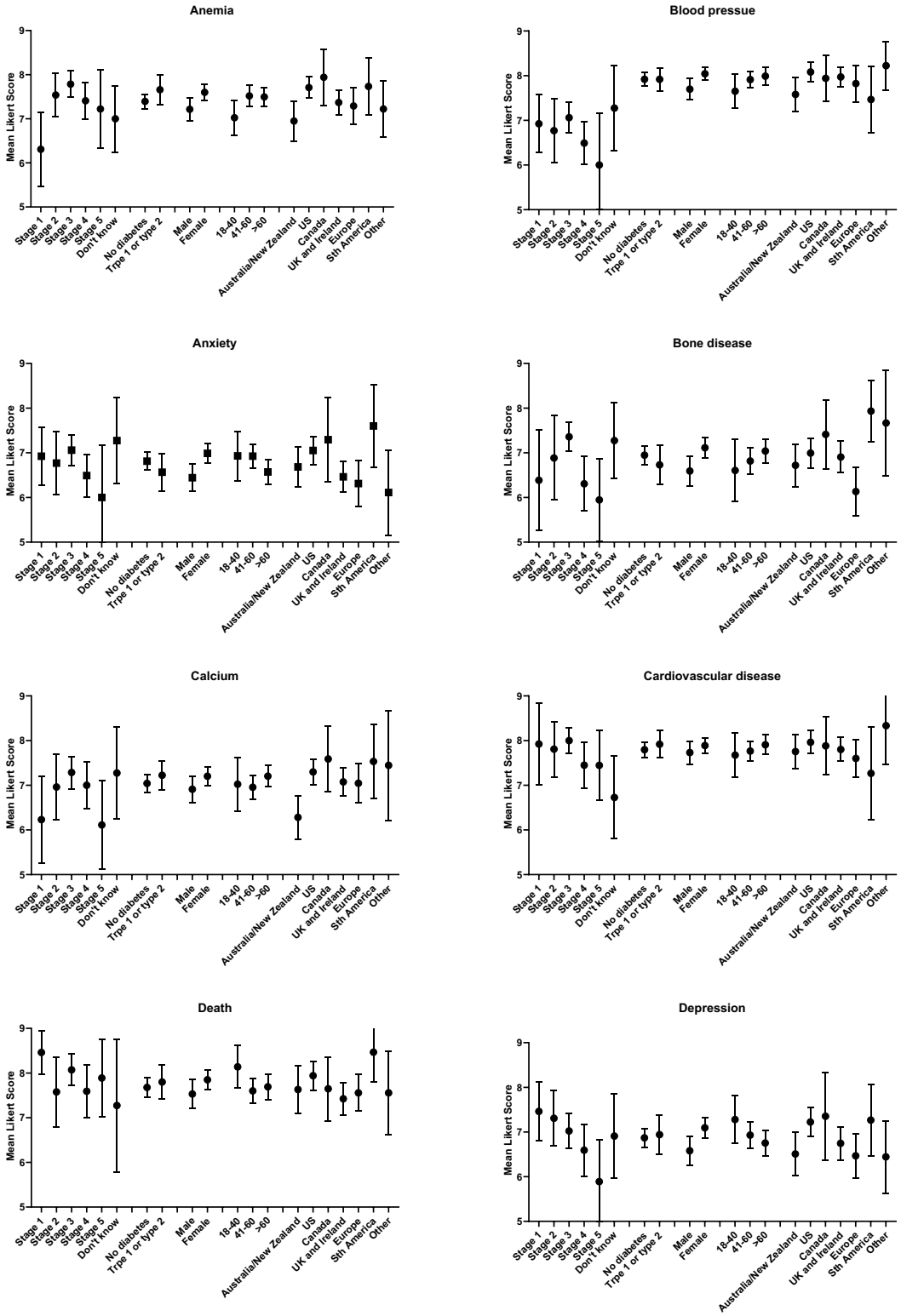
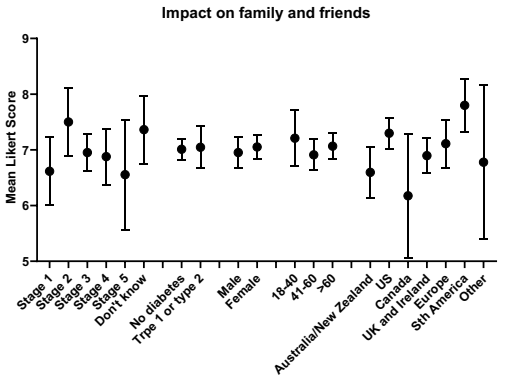
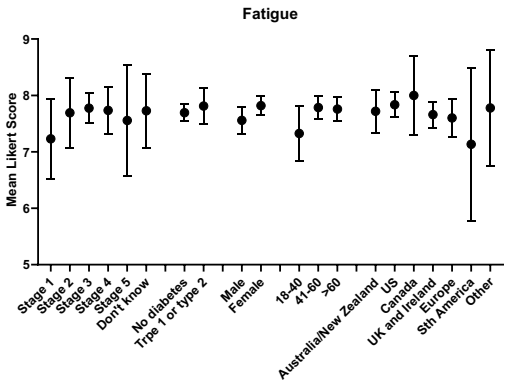
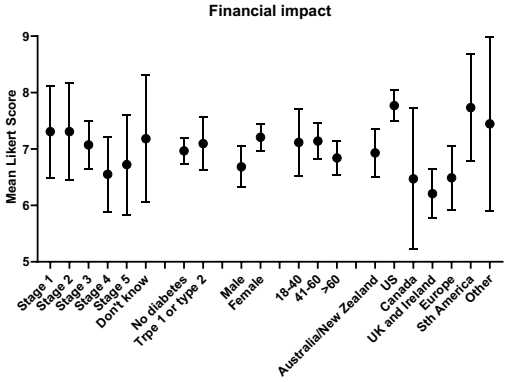
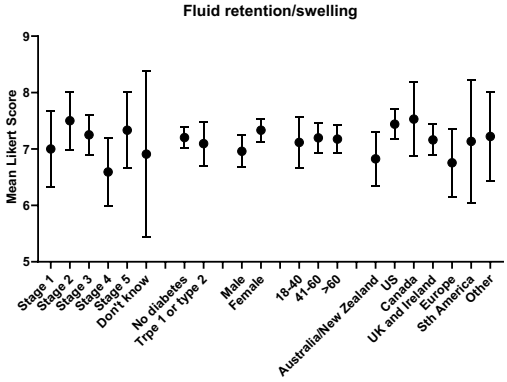


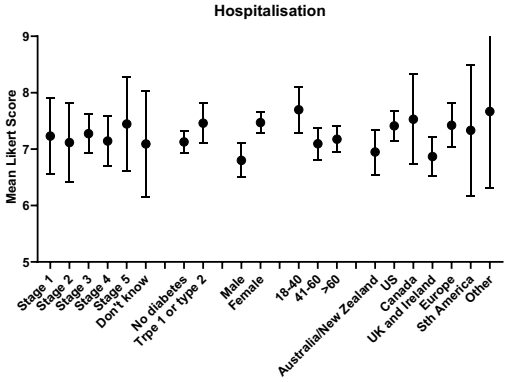
Appendix C

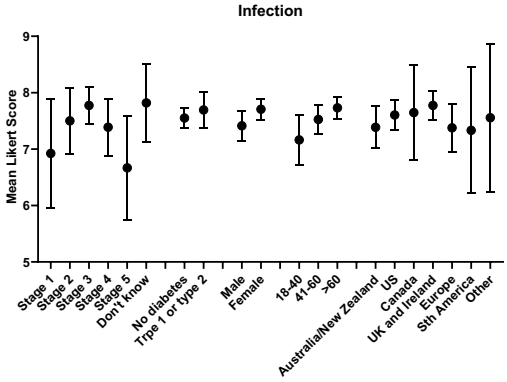

Impact on family and friends
Mean Likert Score
9
8
7
6
5
Stage 1
Stage 2
Stage 3
Stage 4
Stage 5
Don't know
No diabetes
Trpe 1 or type 2
Male
Female
18-40
41-60
>60
Australia/New Zealand
US
Canada
UK and Ireland
Europe
Sth America
Other

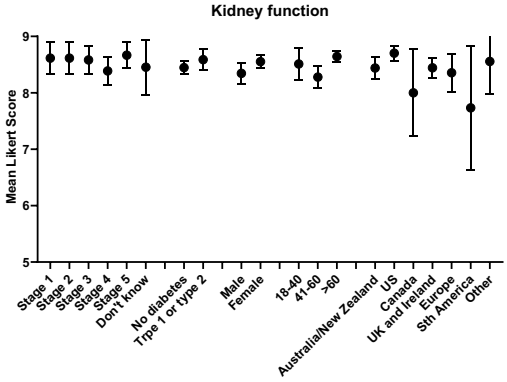

Fatigue
Mean Likert Score
9
8
7
6
5
Stage 1
Stage 2
Stage 3
Stage 4
Stage 5
Don't know
No diabetes
Trpe 1 or type 2
Male
Female
18-40
41-60
>60
Australia/New Zealand
US
Canada
UK and Ireland
Europe
Sth America
Other

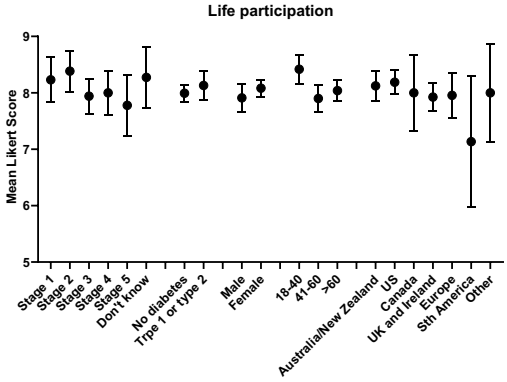

Financial impact
Mean Likert Score
9
8
7
6
5
Stage 1
Stage 2
Stage 3
Stage 4
Stage 5
Don't know
No diabetes
Trpe 1 or type 2
Male
Female
18-40
41-60
>60
Australia/New Zealand
US
Canada
UK and Ireland
Europe
Sth America
Other


Fluid retention/swelling
Mean Likert Score
9
8
7
6
5
Stage 1
Stage 2
Stage 3
Stage 4
Stage 5
Don't know
No diabetes
Trpe 1 or type 2
Male
Female
18-40
41-60
>60
Australia/New Zealand
US
Canada
UK and Ireland
Europe
Sth America
Other

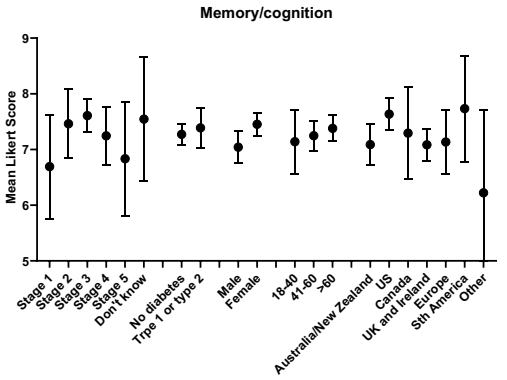

Hospitalisation
Mean Likert Score
9
8
7
6
5
Stage 1
Stage 2
Stage 3
Stage 4
Stage 5
Don't know
No diabetes
Trpe 1 or type 2
Male
Female
18-40
41-60
>60
Australia/New Zealand
US
Canada
UK and Ireland
Europe
Sth America
Other

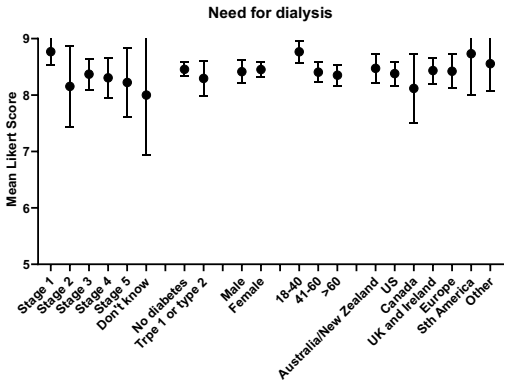

Infection
Mean Likert Score
9
8
7
6
5
Stage 1
Stage 2
Stage 3
Stage 4
Stage 5
Don't know
No diabetes
Trpe 1 or type 2
Male
Female
18-40
41-60
>60
Australia/New Zealand
US
Canada
UK and Ireland
Europe
Sth America
Other

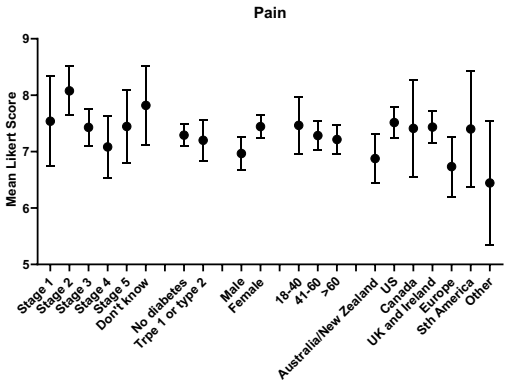

Kidney function
Mean Likert Score
9
8
7
6
5
Stage 1
Stage 2
Stage 3
Stage 4
Stage 5
Don't know
No diabetes
Trpe 1 or type 2
Male
Female
18-40
41-60
>60
Australia/New Zealand
US
Canada
UK and Ireland
Europe
Sth America
Other

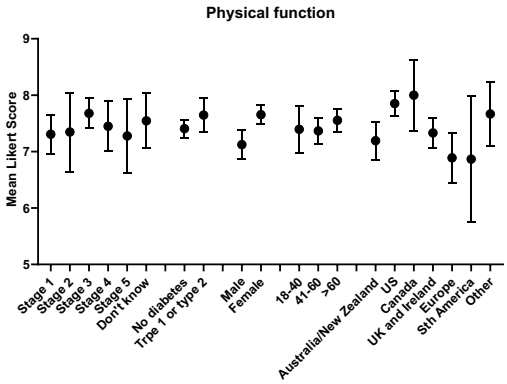

Life participation
Mean Likert Score
9
8
7
6
5
Stage 1
Stage 2
Stage 3
Stage 4
Stage 5
Don't know
No diabetes
Trpe 1 or type 2
Male
Female
18-40
41-60
>60
Australia/New Zealand
US
Canada
UK and Ireland
Europe
Sth America
Other

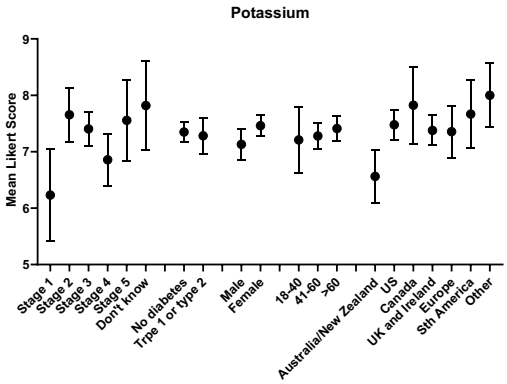
Appendix C

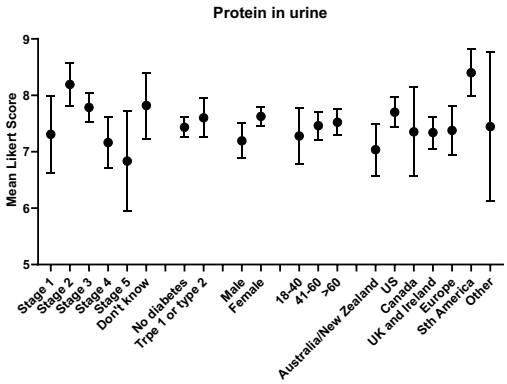

Memory/cognition
Mean Likert Score
9
8
7
6
5
Stage 1
Stage 2
Stage 3
Stage 4
Stage 5
Don't know
No diabetes
Trpe 1 or type 2
Male
Female
18-40
41-60
>60
Australia/New Zealand
US
Canada
UK and Ireland
Europe
Sth America
Other

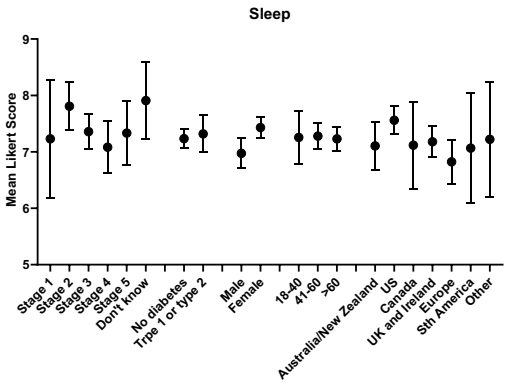

Need for dialysis
Mean Likert Score
9
8
7
6
5
Stage 1
Stage 2
Stage 3
Stage 4
Stage 5
Don't know
No diabetes
Trpe 1 or type 2
Male
Female
18-40
41-60
>60
Australia/New Zealand
US
Canada
UK and Ireland
Europe
Sth America
Other


Pain
Mean Likert Score
9
8
7
6
5
Stage 1
Stage 2
Stage 3
Stage 4
Stage 5
Don't know
No diabetes
Trpe 1 or type 2
Male
Female
18-40
41-60
>60
Australia/New Zealand
US
Canada
UK and Ireland
Europe
Sth America
Other


Physical function
Mean Likert Score
9
8
7
6
5
Stage 1
Stage 2
Stage 3
Stage 4
Stage 5
Don't know
No diabetes
Trpe 1 or type 2
Male
Female
18-40
41-60
>60
Australia/New Zealand
US
Canada
UK and Ireland
Europe
Sth America
Other


Potassium
Mean Likert Score
9
8
7
6
5
Stage 1
Stage 2
Stage 3
Stage 4
Stage 5
Don't know
No diabetes
Trpe 1 or type 2
Male
Female
18-40
41-60
>60
Australia/New Zealand
US
Canada
UK and Ireland
Europe
Sth America
Other


Protein in urine
Mean Likert Score
9
8
7
6
5
Stage 1
Stage 2
Stage 3
Stage 4
Stage 5
Don't know
No diabetes
Trpe 1 or type 2
Male
Female
18-40
41-60
>60
Australia/New Zealand
US
Canada
UK and Ireland
Europe
Sth America
Other


Sleep
Mean Likert Score
9
8
7
6
5
Stage 1
Stage 2
Stage 3
Stage 4
Stage 5
Don't know
No diabetes
Trpe 1 or type 2
Male
Female
18-40
41-60
>60
Australia/New Zealand
US
Canada
UK and Ireland
Europe
Sth America
Other

C.3 Supplementary Table S1. Outcome definitions used in the SONG-CKD Delphi survey.

We want to understand which outcomes you think should be measured and reported in research (clinical trials) in adults with chronic kidney disease who do not require dialysis or kidney transplant. An outcome is something that can change because of a health condition or treatment. Outcomes are measured and reported in clinical trials. We want to make sure that trials report outcomes that are important to you so they can help inform decisions about treatment based on outcomes that matter. Your opinion will help inform the development of "core outcomes" to measure in all trials in people with chronic kidney disease. You will also be able to suggest new outcomes.

Outcome	Definition
Ability to work	Being able to work or do the type of work you want
Anxiety	Feeling anxious or stressed
Appearance	Changes in the way you look, body image
Appetite	Loss or change in appetite, enjoyment of food
Blood pressure	The number to indicate the pressure in the arteries, high (hypertension) or low (hypotension) blood pressure
Bone health	Bone strength or density, risk of fractures
Cancer	Any type of cancer. A disease caused by abnormal cell growth with the potential to invade or spread to other parts of the body
Cardiovascular disease	Disease of the heart and blood vessels (including stroke, heart attack or heart failure)
Cognitive function	Ability to remember things (short and long-term), think clearly, problem solve
Cramping	Painful or uncomfortable contraction or spasms in muscles
Death	Number of people who die, risk of death, how long the patient will live
Depression	Feeling down, low mood, strong and persistent feelings of sadness, hopelessness, despair for most of the time, over a long time
Diabetes	Abnormally high levels of sugar in the blood because the body cannot produce enough insulin or insulin is not working properly
Fatigue	Feeling tired or having no energy for weeks, most of the time
Fertility	Ability to have children
Financial impact	Impact on the person's ability to earn a living, resources, stability and monetary security. Includes insurance and debt
Fluid retention/swelling	An increase in body fluid causing swelling
Hair changes	Abnormal loss or change in the amount or quality of hair (includes too much hair growth and hair loss)
Hospitalization	Staying in hospital for a health problem or complication
Impact on family/friends	Impact of the patient's family, caregivers
Infection	Infectious from any of viruses, bacteria, fungi/yeast or parasites
Intimate relationships and sexual function	Ability to have intimate relationships, desire for and enjoyment of sex
Itch	Dry or itchy skin, irritating sensation that makes a person want to scratch
Joint or muscle pain	Aches or pains in the joints, back and/or muscles
Kidney function	How well kidneys remove 'waste' from the body and balance salt and fluids (could be measured by creatinine in the blood and eGFR)
Life participation	Ability to participate or do daily activities including socialising, study, hobbies
Mobility	Ability to walk, move around and function normally
Mood	Unusual changes in emotion, crying easily, feelings of anger or agitation towards others
Nausea, vomiting	Often feeling like throwing up, retching, sick in the stomach, acid reflux
Need for dialysis or transplant	Reaching end stage kidney disease and needing a kidney transplant or dialysis
Protein in the urine	Level of protein in the urine. This may be a sign of disease activity and/or damage to the filters in the kidney
Relapses	Disease comes back again; 'flares' or recurs – either slowly or suddenly.

Remission	Disease gets better (i.e. partial remission) or goes away (complete remission); either temporarily or for the longer term
Skin changes	Change in skin such as stretch marks, thin skin and acne
Sleep	Trouble getting to sleep, staying asleep or poor quality sleep
Strength and physical functioning	Being able to do physical tasks, feeling strong in the body
Weight change	Loss or gain in body weight (not because of fluid)

Appendix C

C.4 Supplementary Table S2. Round 1 Outcome Scores (mean, median, proportion 7-9 %) of patients/caregivers and health professionals

	Patients/caregivers (n=628)			Health Professionals (n=771)		
	Mean	Median	Proportion 7-9 (%)	Mean	Median	Proportion 7-9 (%)
Anaemia	7.3	8.0	69.4%	7.1	7.0	66.1%
Anxiety	6.6	7.0	54.4%	6.5	7.0	53.1%
Appetite	6.2	6.0	40.6%	6.6	7.0	51.1%
Blood pressure	7.8	8.0	80.9%	7.4	8.0	74.8%
Bone disease	7.0	7.0	61.7%	6.8	7.0	59.5%
Calcium, phosphate or parathyroid hormone	7.1	7.0	59.0%	6.7	7.0	56.6%
Cardiovascular disease	7.5	8.0	77.1%	7.9	8.0	88.5%
Cramping	6.5	7.0	47.8%	6.2	6.0	43.8%
Death	7.7	9.0	73.8%	8.1	9.0	86.5%
Depression	6.8	7.0	61.4%	6.9	7.0	63.1%
Fatigue	7.4	8.0	73.5%	7.1	7.0	65.7%
Fertility	5.3	5.0	27.7%	5.9	6.0	36.3%
Financial impact	7.0	7.0	62.9%	7.1	7.0	67.2%
Fluid retention/swelling	7.0	7.0	64.8%	7.1	7.0	68.2%
Gastrointestinal problems	6.7	7.0	55.1%	6.2	6.0	44.4%
Headaches	6.2	6.0	44.0%	6.0	6.0	37.2%
Hospitalisation	7.0	7.0	60.8%	7.4	8.0	76.0%
Impact on family/friends	6.9	7.0	58.8%	6.9	7.0	59.4%
Infection	7.3	8.0	70.0%	7.0	7.0	63.8%
Itchy skin	6.4	6.0	47.8%	6.5	7.0	49.9%
Kidney function	8.2	9.0	87.4%	7.9	9.0	84.8%
Life participation	7.7	8.0	81.2%	7.6	8.0	78.1%
Memory/Cognition	7.0	7.0	63.8%	6.7	7.0	57.9%
Mood	6.4	7.0	48.8%	6.3	6.0	45.1%
Need for dialysis/transplant	8.2	9.0	86.3%	8.3	9.0	90.1%
Pain	7.1	7.0	67.3%	6.7	7.0	57.3%
Physical function	7.2	7.0	68.6%	7.0	7.0	62.6%
Potassium	7.4	8.0	70.9%	7.0	7.0	63.1%
Protein in the urine	7.5	8.0	72.1%	6.9	7.0	64.5%
Restless legs	6.3	6.0	44.3%	6.2	6.0	39.0%
Sexual function	6.1	6.0	39.8%	6.3	6.0	42.6%
Sleep	7.0	7.0	64.5%	6.7	7.0	54.9%
Weight	6.4	7.0	50.7%	6.3	6.0	45.4%

Appendix C

C.5 Supplementary Table S3. Round 2 Outcome Scores (mean, median, proportion 7-9 %) of patients/caregivers and health professionals

	Patients/caregivers (n=383)			Health Professionals (n=407)		
	Mean	Median	Proportion 7-9 (%)	Mean	Median	Proportion 7-9 (%)
Anaemia	7.5	8.0	75.2%	6.9	7.0	63.9%
Anxiety	6.8	7.0	57.7%	6.5	7.0	53.2%
Blood pressure	7.9	8.0	86.7%	7.5	8.0	82.1%
Bone disease	6.9	7.0	62.0%	6.6	7.0	56.7%
Calcium, phosphate or parathyroid hormone	7.1	7.0	63.4%	6.4	6.0	47.0%
Cardiovascular disease	7.8	8.0	82.1%	8.2	8.0	95.0%
Death	7.7	9.0	77.0%	8.4	9.0	92.5%
Depression	6.9	7.0	65.5%	7.1	7.0	71.1%
Impact on family/friends	7.0	7.0	64.5%	6.9	7.0	60.9%
Fatigue	7.7	8.0	85.0%	7.4	7.0	75.9%
Financial impact	7.0	7.0	65.4%	7.2	7.0	68.9%
Fluid retention/swelling	7.2	7.0	70.3%	7.0	7.0	71.3%
Hospitalisation	7.2	7.0	68.7%	7.6	8.0	81.9%
Infection	7.6	8.0	78.9%	7.2	7.0	70.5%
Kidney function	8.5	9.0	95.4%	8.3	9.0	92.4%
Life participation	8.0	8.0	86.9%	8.0	8.0	87.6%
Memory/Cognition	7.3	8.0	75.7%	7.0	7.0	68.0%
Need for dialysis/transplant	8.4	9.0	90.9%	8.6	9.0	96.8%
Pain	7.3	8.0	72.7%	7.0	7.0	68.0%
Physical function	7.5	8.0	80.5%	7.1	7.0	69.8%
Potassium	7.3	7.0	73.8%	6.8	7.0	61.4%
Protein in the urine	7.5	8.0	76.0%	6.8	7.0	64.6%
Sleep	7.3	7.0	72.7%	6.8	7.0	60.1%

Appendix C

C.6 Supplementary Table S4. Round 2 mean scores of patients/caregivers and health professionals by language (English, Spanish and French)

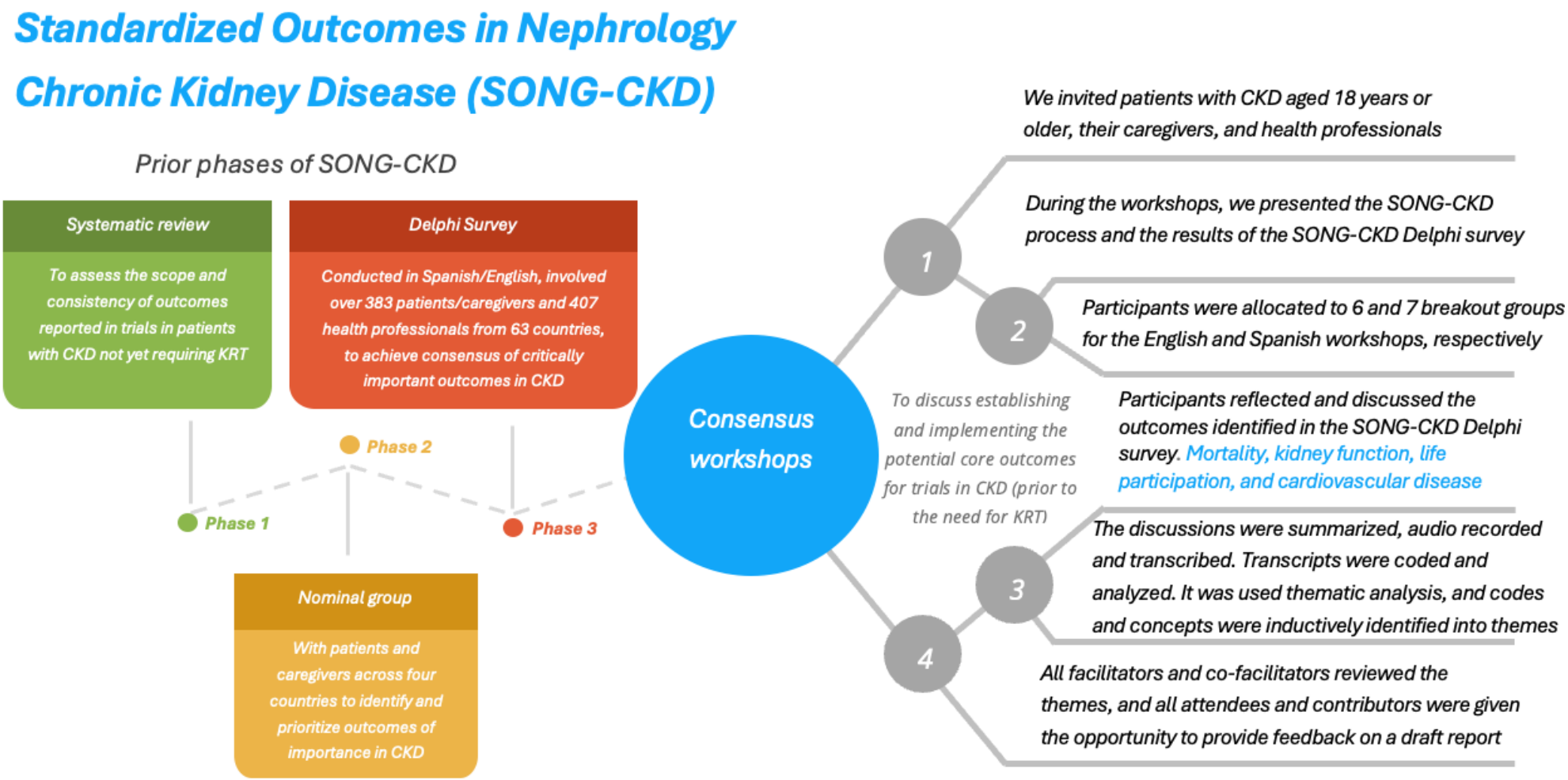
	Patients/caregivers			Health Professionals		
	English n=342	Spanish n=23	French n=18	English n=321	Spanish n=33	French n=33
Anaemia	7.5	7.7	7.2	6.8	7.7	7.1
Anxiety	6.7	7.6	6.0	6.5	7.0	6.3
Blood pressure	7.9	7.5	8.0	7.4	8.2	7.7
Bone disease	6.9	7.4	5.6	6.5	7.7	6.5
Calcium, phosphate or parathyroid hormone	7.1	7.5	7.2	6.2	7.7	6.7
Cardiovascular disease	7.8	7.7	7.6	8.1	8.4	8.2
Death	7.7	8.4	7.3	8.4	8.7	8.3
Depression	6.9	7.2	6.1	7.1	7.8	6.8
Impact on family/friends	7.0	7.4	7.2	6.8	7.6	6.8
Fatigue	7.8	7.3	7.7	7.3	7.7	7.4
Financial impact	7.0	7.5	6.4	7.1	8.0	7.0
Fluid retention/swelling	7.2	7.1	6.7	6.9	7.7	7.0
Hospitalisation	7.2	7.6	7.3	7.5	8.2	7.6
Infection	7.6	7.2	7.3	7.2	7.7	6.9
Kidney function	8.5	7.9	8.4	8.3	8.5	8.2
Life participation	8.1	7.2	7.9	8.0	8.2	7.6
Memory/Cognition	7.3	7.4	6.7	7.0	7.3	6.6
Need for dialysis/transplant	8.4	8.6	8.7	8.5	8.7	8.6
Pain	7.3	7.3	6.0	7.0	7.6	6.9
Physical function	7.5	7.0	6.9	7.1	7.3	7.1
Potassium	7.3	8.0	7.3	6.6	7.8	7.3
Protein in the urine	7.4	8.3	7.4	6.7	7.4	7.1
Sleep	7.3	7.0	6.4	6.8	7.4	6.7

Appendix C

C.7 Supplementary Table S5. List of new outcomes suggested by participants

New outcomes suggested	Number of respondents who suggested the outcome
Acidosis	18
Acute kidney injury	4
Body image	8
Isolation and loneliness	2
Diabetes and blood sugar control	11
Nausea and vomiting	6

D.1 Supplementary Figure S1: Prior phases of SONG-CKD Workshop Report Schema.



D.2 Supplementary Table S1: SONG-CKD Consensus Workshop Investigators for group authorship

Name	Organization	Country
Adam Martin	The Children's Hospital at Westmead	Australia
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Alejandro Ferreiro	Sociedad Latinoamericana de Nefrología	Uruguay
Alejandro Sepulveda	Centro de nutrición cardiorrenal	Chile
Ali Abu-Alfa	University of Beirut	Lebanon
Alice Smith	Leicester General Hospital	UK
Alison Burns	Not applicable	UK
Aliza Thompson	FDA	US
Allison Jaure	The University of Sydney	Australia
Amanda Sluiter	The University of Sydney	Australia
Amelie Bernier-Jean	The University of Sydney	Canada
Amer Joseph	Bayer	Germany
Ana Lucia Diez de Sollano	Not applicable	Mexico
Ana Lohaus	Not applicable	Chile
Anastasia Hughes	The University of Sydney	Australia
Andrea Aranda	Sociedad Chilena de Nefrología	Chile
Andrea Matus Gonzalez	The University of Sydney	Australia
Andrea Viecelli	University of Queensland	Australia
Andrew Levey	Tufts Medical Center	US
Angela Ju	The University of Sydney	Australia
Angela Wang	The University of Hong Kong	Hong Kong
Anita Levia Lohaus	Not applicable	Chile
Ankit Sharma	The University of Sydney	Australia
Armando Teixeira-Pinto	The University of Sydney	Australia
Arturo Ortega Robledo	Not applicable	Mexico
Ayano Kelly	The University of Sydney	Australia
Beatriz Aedo	Not applicable	Chile
Ben Bartlett	Not applicable	Australia
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Benedicte Stengel	INSERM	France
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Brenda Hemmelgarn	University of Alberta	Canada
Brooke Huuskes	LaTrobe University	Australia
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Catherine Campbell	Not applicable	US
Cecile Couchoud	REIN Registry, Saint-Denis la Plaine	France
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Chandana Guha	The University of Sydney	Australia
Charlotte Kirkpatrick	Not applicable	UK
Chelita Riveros	Not applicable	Chile
Christoph Wanner	University Hospital of Würzburg,	Germany
Claudia Camacho	Not applicable	US
Cristobal Rigo-Righi	Not applicable	Chile
Daniel Gallego	ALCER	Spain
David Wheeler	University College London	UK
Denis Fouque	University of Lyon	France
Dominik Steubl	Boehringer Ingelheim International	
Donna Caissie	Not applicable	US
Eduardo Lorca	University of Chile	Chile
Elena Bavlovlenkov	CMS	US
Elise Gouin	Tours University	France
Elvia Vargas y Javiera Barriga	Not applicable	Chile
Emanuelle Orr	Not applicable	UK
Emma O'Lone	The University of Sydney	Australia
Eric Au	The University of Sydney	Australia
Erika Hernández Valverde	Not applicable	Mexico
Esteban Hinojosa	Not applicable	Chile
Fernanda Espinoza	Not applicable	Chile
Fabian Muñoz	Not applicable	Chile
Gareth Hughes	Not applicable	UK
Gino Buono Core	Not applicable	Chile
Giovanna Carrillo	Not applicable	Chile
Gloria Ashuntantang	University of Yaounde	Cameroon
Greg Wilson	University of Queensland	Australia
Gregorio (Tomas) Obrador	Universidad Panamericana	Mexico
Guillermo Moraga Crisóstomo	Not applicable	Chile
Harold Feldman	University of Pennsylvania	US
Haydee Mellado	Clínica Dávila	Chile
Hector Gonzalez	Not applicable	Mexico
Henning Sondergaard	Danish Kidney Foundation	Denmark
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Hilaria Camacho	Not applicable	Mexico
Ian De Boer	University of Washington	US
Ian Williamson	Not applicable	Australia
Ikechi Okpechi	University of Cape Town	South Africa
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Jasna Fabiola Aguirre Arancibia	Not applicable	Chile
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Joan Jaure	Not applicable	Australia
John Gill	University of British Columbia	Canada
Jon Barrett	University of Leicester	UK
Jonathan Craig	Flinders University	Australia
Jonathan Garay	Sociedad de Nefrología	Chile
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Karine Manera	The University of Sydney	Australia
Karla Costilla	Not applicable	US
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Katherine Widders	Not applicable	Australia
Katherinne Diaz	Not applicable	Chile
Kieran McCaffery	University of London	UK
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Laura Sola	University of the Republic Uruguay	Uruguay
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Lilia Cervantes	Denver Hospital	US
Linda Egan	Not applicable	Australia
Lorena Camacho	Not applicable	Mexico
Lorena Sandino	Centro de nutrición cardiorrenal	Chile
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Luis Arroyo	Not applicable	Guatemala
Luis Enrique Cavazos Siller	Not applicable	Mexico
Luca Torrisi	The University of Sydney	Australia
Luisa Miniaci	Not applicable	Canada
Macarena Arancibia	Centro de nutrición cardiorrenal	Chile
Magdalena Madero	National Heart Institute	Mexico
Maggie Ma	Not applicable	Hong Kong
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Marco A Muñoz M	Not applicable	Chile
Margaret Gebauer	Not applicable	US
Maria de los Angeles Bravo	Corporación Municipal de la Florida	Chile
María Jose Pimentel-Ricardo Soto	Not applicable	Chile
Maria Lourdes Pérez Islas	Not applicable	Mexico
Mario Ruiz Castellanos	Not applicable	Mexico
Marisel Lobos R.	Not applicable	Chile
Marisol Robles	Not applicable	Mexico
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Melissa Nataatmadja	University of Queensland	Australia
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Nancy Quezada	Not applicable	Chile
Nelson Calisto	Not applicable	Chile
Nicole Evangelidis	The University of Sydney	Australia
Nicole Scholes-Robertson	The University of Sydney	Australia
Noa Amir	The University of Sydney	Australia
Paola Salas	Not applicable	Chile
Patrick Rossignol	University of Lorraine	France
Patrizia Natale	The University of Sydney	Australia
Paulina Figueroa	Not applicable	Chile
Paulina Raquel Rodriguez	Not applicable	Mexico
Pernille Henman	Not applicable	Denmark
Peter Reeves	Not applicable	Australia
Peter Rossing	Steno Diabetes Centre	Denmark
Peter Tugwell	University of Ottawa	Canada
Rafael Gomez	Universidad del Valle	Colombia
Raj Manhas	Not applicable	India
Rebecca Goodwin	NIH	US
Rebecca Wu	The University of Sydney	Australia
Refugio, Ana Sofia, Ana Bertha Camacho Sanchez	Not applicable	Mexico
Rekha Kambhampati	FDA	US
Ricardo Andrade Millacura	Not applicable	Chile
Richard Roderick	Not applicable	US
Robert Star	NIDDK NIH	US
Roberto Pecoits-Filho	School of Medicine, Catholic University of Paran	Brazil
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Ron Wald	University of Toronto	Canada
Rosanna Cazzolli	The University of Sydney	Australia
Sally Crowe	Crowe Associates Ltd	UK
Samaya Anumudu	Baylor College of Medicine	US
Samuel Fung	Princess Margaret Hospital	Hong Kong
Sara Sundstrom	Not applicable	Australia
Sebastian Cabrera	University of Chile	Chile
Shyam Mythuramalingam	South Australian Medical Research Institute	Australia
Simon Carter	The University of Sydney	Australia
Soledad Molina	Sociedad de Nefrología	Chile
Sybille Hauske	Boehringer-ingelheim.com	Germany
Tamara Bórquez	Hospital Regional de Concepción Dr. Guillermo Grant Benavente.	Chile
Tess Harris	PKD International	UK
Thorsten Vetter	European Medicines Agency	Netherlands
Thyago Moraes	Pontifícia Universidade Católica do Paraná	Brazil
Tim Usherwood	The University of Sydney	Australia
Tom Vastani	The University of Sydney	Australia
Veronica Godoy Hernandez	Not applicable	Chile

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Vivek Jha	The George Institute for Global Health	India
Will Herrington	Oxford University	UK
Wim van Biesen	Ghent University	Belgium
Wolfgang Winkelmayer	Baylor College of Medicine	US
Ximena Atilano	Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán	Mexico
Ximena Gallinato	Not applicable	Chile
Yeoungjee Cho	University of Queensland	Australia
Yolanda Pichon	Not applicable	Mexico

D.3 Supplementary Item 1: Facilitator question guide for breakout discussion

Workshop 1 | Online English Workshop

1. Do you agree with the core outcomes for CKD? Are they relevant to different populations and settings? Are they relevant across all stages of CKD – 1 to 5, different levels of kidney function? Are they relevant across different types (diagnosis and causes) of CKD?
2. What does life participation mean for people with CKD?
3. How can the core outcomes set be implemented in all trials in CKD?

Workshop 2 | Online Spanish Workshop

1. Está de acuerdo este set de resultados clínicos (función renal, actividades de la vida diaria, enfermedad cardiovascular, muerte) en personas con Enfermedad Renal Crónica (ERC) antes de la necesidad de diálisis/trasplante)? Tiene relevancia para diferentes poblaciones (características sociodemográficas), para todas las etapas de la ERC 1a 5, y según las diferentes causas o diagnósticos.
2. La enfermedad renal avanzada (que requiere diálisis/trasplante) se va a integrar como parte de la función renal (según se determina en otras corrientes de SONG)
3. La importancia de la presión arterial está relacionada con las enfermedades cardiovasculares y la función renal, que se ya se encuentran en los resultados centrales propuestos. Según los datos de este estudio SONG-CKD y de los estudios SONG anteriores.

Appendix E

E.1 Supplementary File 1. Life Participation Workshop Investigators List

Name	Primary Affiliation	Country
CKD Life participation expert working group		
Adeera Levin	University of British Columbia	Canada
Anastasia Hughes	The University of Sydney	Australia
Andrea Matus Gonzalez	The University of Sydney	Australia
Fergus Caskey	Bristol University	UK
Meghan Elliot	University of Calgary	Canada
Janine Farragher	University of Toronto	Canada
Sharlene Greenwood	Kings College London	UK
Amanda Sluiter	The University of Sydney - Patient	Australia
Hernan Trimarchi	Universidad Católica Argentina	Argentina
Bill Wang	International Society of Nephrology - Patient	China
Workshop participants and contributors		
Adeera Levin	University of British Columbia	Canada
Alejandro Ferreiro	Facultad de Medicina, Universidad de la República., Programa de Salud Renal de Uruguay, Montevideo	Uruguay
Alejandro Sepulveda	Cardiorenal Nutrition Center, Santiago, Chile	Chile
Allison Jaure	The University of Sydney	Australia
Anastasia Hughes	The University of Sydney	Australia
Andrea Viecelli	University of Queensland	Australia
Andrea Matus Gonzalez	The University of Sydney	Australia
Brooke M Huuskes	La Trobe University - Patient	Australia
Chandana Guha	The University of Sydney - Caregiver	Australia
Claudio Mascheroni	Servicio de Nefrología San Pedro. Bs As. Universidad Nacional de Rosario, Argentina	Argentina
Eduardo Lorca	Eastern Department of Internal Medicine, Faculty of Medicine, University of Chile, and Hospital del Salvador Nephrology Service, Santiago de Chile	Chile
Germaine Wong	The University of Sydney	Australia
Haydee Mellado	Clinica Davila	Chile
Hernan Trimarchi	Nephrology Service and Kidney Transplant Unit, Hospital Británico de Buenos Aires, Argentina	Argentina
Laura Sola	Latin American Society of Nephrology and Hypertension-SLANH, Panama City, Panama; and Hemodialysis Center-CASMU-IAMPP, Montevideo, Uruguay	Uruguay
Lilia Cervantes	Division of Hospital Medicine, Department of Medicine, University of Colorado, School of Medicine	USA
Linda Weng	Servicio de Nefrología San Pedro. Bs As. Argentina	Argentina
Macarena Arancibia Garcia	Cardiorenal Nutrición Center, Santiago, Chile	Chile
Matias Monkowski	Nephrology Service and Kidney Transplant Unit, Hospital Británico de Buenos Aires, Argentina	Argentina
Mauro Lampo	Nephrology Service and Kidney Transplant Unit, Hospital Británico de Buenos Aires, Argentina	Argentina
Soledad Molina	Patient	Chile
Adriana Alsogaray	Patient	Argentina
Aldana Marrero	Caregiver	Uruguay
Alejanedro Torres	Patient	Argentina
Alicia Susana Ferrari	Caregiver	Argentina
Alma Molas	Patient	Argentina
Ana Malvar	Hospital Fernández, Nephrology Unit, Buenos Aires, Argentina	Argentina
Candela Leguizamon	Patient	Argentina
Carlos Gonzalez	Caregiver	Chile
Carlos Rivadeneira	Caregiver	Argentina
Celecte Caceres	Patient	Argentina
Claudia Mansilla	Patient	Argentina
Claudio Cirelli	Caregiver	Argentina
Daniela Calvo	Patient	Argentina

Elizabeth Troncoso	Patient	Chile
Erika Ameku	Patient	Argentina
Federico Fuentes	Patient	Argentina
Fernando Balieiro	Patient	Chile
Hernán Lanzillotta	Patient	Argentina
Hija (Liliana Tapia)	Caregiver	Argentina
Horacio Marcelo González	Caregiver	Argentina
Humberto Gilabert	Patient	Argentina
Jorge Spinelli	Patient	Argentina
Laura Torres	Patient	Argentina
Lautaro de Vedia	Caregiver	Argentina
Leonardo Garateguy	Patient	Argentina
Lourdes Leguizamon	Patient	Argentina
Luis Ayala	Caregiver	Chile
Marcela Briones	Patient	Chile
Marcela Martínez	Caregiver	Argentina
Maria Carolina	Patient	Chile
María del Carmen Lombardo	Caregiver	Argentina
Maria Del Carmen Toto	Caregiver	Argentina
Maria Eugenia Rotundo	Patient	Argentina
Maria Galarza	Patient	Argentina
Maria Laura Montes de Oca	Patient	Argentina
Maria Martha Vera	Patient	Argentina
Maria Valera	Caregiver	Argentina
Maria Victoria Recabarren	Patient	Argentina
Mariana Flaherty	Caregiver	Argentina
Marianela Sierra Canales	Patient	Argentina
Marta Busto	Caregiver	Argentina
Mercedes López Marcote	Patient	Argentina
Natalia Congestri	Caregiver	Argentina
Noemi Espinola	Patient	Argentina
Noemí Mercedes Marcote	Caregiver	Argentina
Norma Hernandez	Patient	Argentina
Nubia Valenzuela	Caregiver	Chile
Paula Farías	Patient	Argentina
Roberto Luis Calvo	Caregiver	Argentina
Rolando Claure-Del Granado	Division of Nephrology, Department of Medicine, Hospital Obrero; Caja Nacional de Salud, Universidad Mayor de San Simon School of Medicine, Cochabamba, Bolivia	Bolivia
Silvana Sogos	Caregiver	Argentina
Wilmer Jim Escobar Torres	Centro Nacional de Salud Renal	Peru
Yanina Vilariño	Patient	Argentina

Appendix E

E.2 Supplementary File 2. Facilitator question guide for breakout discussion:

1. Has CKD impacted your ability to participate in life activities – in what way? What did this mean for you?
2. What are the barriers and facilitators to life participation for patients with chronic kidney disease?
3. What could help to improve life participation in patients with CKD?

Guía de preguntas para el facilitador en el debate en grupos:

1. ¿Ha impactado la enfermedad renal en su capacidad para participar de las actividades de la vida? ¿De qué manera? ¿Qué ha significado esto para usted?

2. ¿Cuáles son las barreras y los catalizadores para la realización de actividades de la vida diaria de los pacientes con enfermedad renal crónica?

3. ¿Qué podría ayudar a mejorar la realización de actividades de la vida diaria en los pacientes con enfermedad renal crónica?