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the example of advanced CKD in the elderly

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**Understanding generalisability, and
issues of recruitment in cohort studies:
the example of advanced CKD in the
elderly**

Dr Anirudh Rao

**A dissertation submitted to the University of Bristol in
accordance with the requirements for the award of the
degree of PhD in the Faculty of Health Sciences, School of
Social and Community Medicine (May 2018)**

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Abstract

ABSTRACT

Introduction: Observational studies play a valuable role in nephrology and have informed clinical practice. A significant challenge to observational research is external validity. Threats to generalisability can occur at the design stage due to selective inclusion criteria, at the recruitment stage due to non-participation of specific groups, and finally at the reporting stage due to poor reporting.

Methods: The PhD thesis was a mixed method study of convergent parallel/ triangulation design, embedded into European QUALity Study on treatment in advanced chronic kidney disease (EQUAL). The thesis involved three studies: quantitative, qualitative and systematic review to understand more fully the various factors that could affect a study's generalisability at the design, recruitment and reporting stages respectively. The quantitative arm was a retrospective observational study comparing patients in primary and secondary care meeting the same inclusion criteria as EQUAL. The qualitative arm involved semi-structured interviews with patients who agreed and did not agree to participate in EQUAL. The systematic review assessed the quality of reporting of cohort studies before (1/1/2002-31/12/2007) and after (1/10/2008-31/12/2013) the publication of the STROBE statement.

Results: The quantitative arm of the thesis showed that patients in EQUAL were more likely to be younger, male and from an urban setting compared to the primary and secondary care cohort patients. Overall lesser co-morbidity of EQUAL patients meant that they were more likely to be alive at one year or to be admitted to hospital for illnesses. In the qualitative arm of the thesis, patients who agreed to participate in research reported being activated in their healthcare, and this seemed to relate to their decision to take part in research. Altruistic morals had a strong influence on participation in EQUAL study. The issue of caring responsibility and transportation were the main reasons causing inconvenience and negatively influenced participation. The systematic review showed that there had been an improvement in the overall reporting quality of CKD cohort studies particularly in the latter three years of the post-STROBE period.

Conclusion: The mixed methods approach of this PhD thesis aided a breadth and depth of understanding of some of the issues affecting generalisability with corroboration of the results from the quantitative and qualitative arms of the study. Sustained efforts of researchers are required to improve the generalisability of research findings at every stage of observational research.

Author's Declaration

AUTHOR'S DECLARATION

I declare that the work in this dissertation was carried out in accordance with the requirements of the University's Regulations and Code of Practice for Research Degree Programmes and that it has not been submitted for any other academic award. Except where indicated by specific reference in the text, the work is the candidate's own work. Work done in collaboration with, or with the assistance of, others, is indicated as such. Any views expressed in the dissertation are those of the author.

SIGNED:

DATE:.....

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List of Abbreviations

List of Publications

Publications Arising from the Thesis

1. **Rao A**, Bruck K, Methven S, Evans R, Stel VS, Jager KJ, et al. Quality of Reporting and Study Design of CKD Cohort Studies Assessing Mortality in the Elderly Before and After STROBE: A Systematic Review. *PLoS One*. 2016;11(5): e0155078.

Other Publications

1. MWM van de Luijngaarden, **A Rao**, KJ Jager et al. on behalf of the EQUAL Study investigators. Uraemic symptom burden and clinical condition in women and men of 65 years of age and older with advanced CKD: results from the EQUAL study. *Nephrology Dialysis Transplantation*.
2. Gilg J, **Rao A**, Fogarty D. UK Renal Registry 16th annual report: chapter 1 UK renal replacement therapy incidence in 2012: national and centre-specific analyses. *Nephron Clinical practice*. 2013;125(1-4):1-27.
3. Gilg J, **Rao A**, Fogarty D. UK Renal Registry 15th annual report: Chapter 1 UK RRT incidence in 2011: national and centre-specific analyses. *Nephron Clinical practice*. 2013;123 Suppl 1:1-28.
4. **Rao A**, Gilg J, Williams A. UK Renal Registry 15th annual report: Chapter 6 haemoglobin, ferritin and erythropoietin amongst UK adult dialysis patients in 2011: national and centre-specific analyses. *Nephron Clinical practice*. 2013;123 Suppl 1:125-50.
5. **Rao A**, Gilg J, Williams A. UK Renal Registry 16th annual report: chapter 10 haemoglobin, ferritin and erythropoietin amongst UK adult dialysis patients in 2012: national and centre-specific analyses. *Nephron Clinical practice*. 2013;125(1-4):183-208.
6. **Rao A**, Pitcher D, Farrington K. UK Renal Registry 16th annual report: chapter 11 blood pressure profile of prevalent patients receiving renal replacement therapy in 2012: national and centre-specific analyses. *Nephron Clinical practice*. 2013;125(1-4):209-18.
7. **Rao A**, Steenkamp R, Caskey F. UK Renal Registry 16th annual report: chapter 5 comorbidities and current smoking status amongst patients starting renal replacement therapy in England, Wales and Northern Ireland from 2011 to 2012. *Nephron Clinical practice*. 2013;125(1-4):99-110.
8. Gilg J, Evans R, **Rao A**, Williams AJ. UK Renal Registry 17th Annual Report: Chapter 7 Haemoglobin, Ferritin and Erythropoietin amongst UK Adult Dialysis Patients in 2013: National and Centre-specific Analyses. *Nephron*. 2015;129 Suppl 1:143-67.
9. Pitcher D, **Rao A**, Caskey F, Davies J, Crowley L, Fluck R, et al. UK Renal Registry 17th Annual Report: Chapter 12 Epidemiology of Reported Infections amongst Patients Receiving Dialysis for Established Renal Failure in England in 2012 to 2013: a Joint Report from Public Health England and the UK Renal Registry. *Nephron*. 2015;129 Suppl 1:257-65.

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10. **Rao A**, Casula A, Castledine C. UK Renal Registry 17th Annual Report: Chapter 2 UK Renal Replacement Therapy Prevalence in 2013: National and Centre-specific Analyses. *Nephron*. 2015;129 Suppl 1:31-56.
11. **Rao A**, Pitcher D, Fluck R, Kumwenda M. UK Renal Registry 17th Annual Report: Chapter 10 2013 Multisite Dialysis Access Audit in England, Northern Ireland and Wales and 2012 PD One Year Follow-up: National and Centre-specific Analyses. *Nephron*. 2015;129 Suppl 1:223-45.
12. Steenkamp R, **Rao A**, Roderick P. UK Renal Registry 17th Annual Report: Chapter 5 Survival and Cause of Death in UK Adult Patients on Renal Replacement Therapy in 2013: National and Centre-specific Analyses. *Nephron*. 2015;129 Suppl 1:99-129.
13. Gilg J, **Rao A**, Williams AJ. UK Renal Registry 18th Annual Report: Chapter 8 Haemoglobin, Ferritin and Erythropoietin amongst UK Adult Dialysis Patients in 2014: National and Centre-specific Analyses. *Nephron*. 2016;132 Suppl 1:169-94.
14. **Rao A**, Evans R, Wilkie M, Fluck R, Kumwenda M. UK Renal Registry 18th Annual Report: Chapter 11 2014 Multisite Dialysis Access Audit in England, Northern Ireland and Wales and 2013 PD One Year Follow-up: National and Centre-specific Analyses. *Nephron*. 2016;132 Suppl 1:253-78.

Presentations to Learned Societies Arising from the Thesis

1. Oral Presentations

- i) STROBE and the quality of reporting observational studies in nephrology
53rd ERA-EDTA Congress, Vienna, Austria, (May 2016)
Crosstalk in renal epidemiology-Presented by Dr Fergus Caskey

2. Poster Presentations (All posters first authored and presented by A Rao)

- i) Using Primary Care Database to Understand the Generalisability of the European QUALity (EQUAL) Study in the UK
ASN Kidney Week 2016, Chicago, USA (Nov 2016)
<https://www.asn-online.org/education/kidneyweek/archives/>
- ii) Factors Affecting Secondary Care Referral of Older People with Advanced Chronic Kidney Disease and Their Outcomes: An Observational Cohort Study
ASN Kidney Week 2016, Chicago, USA (Nov 2016)
<https://www.asn-online.org/education/kidneyweek/archives/>
- iii) Understanding patients' perspectives influencing participation within the EQUAL study in the UK – A qualitative study.
53rd ERA-EDTA Congress, Vienna, Austria, (May 2016) (doi: 10.1093/ndt/gfw198.53)
http://ndt.oxfordjournals.org/content/31/suppl_1/i552.2.full
- iv) Quality of reporting of CKD cohort studies before and after STROBE: A Systematic Review.
52nd ERA-EDTA Congress, London, UK, (May 2015) (doi: 10.1093/ndt/gfv175.20)
http://ndt.oxfordjournals.org/content/30/suppl_3/iii181.2.full

List of Abbreviations

List of Abbreviations

The following table describes the commonly used abbreviations and acronyms used throughout the thesis. The page on which each one is defined or first used is also given.

AKI	A cute K idney I njury	21
BNF	B ritish N ational F ormulary	88
CHD	C oronary H eart D isease	38
CKD	C hronic K idney D isease	21
DOPPS	D ialysis O utcomes and P ractice P atterns Study	68
eGFR	E stimated G lomerular F iltration R ate	21
EPR	E lectronic P atient R ecord	72
EQUAL	E uropean Q UALity Study on treatment in advanced chronic kidney disease	46
ERF	E stablished R enal F ailure	21
ESRD	E nd S tage R enal D isease	30
GP	G eneral P ractices	72
KDIGO	K idney D isease I mproving G lobal O utcomes	23
MDRD	M odification of D iet in R enal D isease	22
MI	M yo C ardial I nfarction	38
NICE	N ational I nstitute of H ealth and C are E xcellence	22
NHS	N ational H ealth S ervice	31
PRD	P rietary R enal D isease	51
RRT	R enal R eplacement T herapy	22
RCT	R andomised C ontrol T rial	33
STROBE	S Trengthening the R eporting of O Bservational studies in E pidemiology	46
UKRR	U K R enal R egistry	98
THIN	T he H ealth I mprovement N etwork	72
CCI	C harlson C omorbidity I ndex	89

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CHAPTER 1. INTRODUCTION

This chapter describes the two essential contexts of the thesis: Chronic Kidney Disease (CKD); and issues around generalisability. The chapter begins by describing the importance of CKD, its epidemiology and the increase in research to prevent CKD progression. This chapter also outlines the challenges of conducting research in patients with CKD and the need for proper research which should produce knowledge or evidence that applies to patients beyond the setting in which it was carried out (generalisability). This chapter discusses the threats to generalisability at various stages of research. It concludes by providing the aims, objectives and a plan of the thesis.

1.1. *Chronic Kidney Disease*

1.1.1. Definition

The term Chronic Kidney Disease (CKD) encompasses some previously used terms, such as “chronic renal failure”, “chronic renal insufficiency” and “chronic kidney impairment”. The definition of CKD is “ the presence of kidney damage (usually detected by urinary protein) or reduced kidney function (defined as estimated glomerular filtration rate [eGFR] <60 mL/min/1.73 m²) for greater than three months, irrespective of the aetiology.” (1) The persistence of reduced kidney function for at least three months is necessary to distinguish CKD from acute kidney injury (AKI). CKD is often associated with a progressive reduction in kidney function over a period of time, culminating for some in established renal failure (ERF) or end-stage kidney disease (ESKD) which requires treatment with

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comprehensive conservative care or renal replacement therapy (RRT) in the form of dialysis or transplantation.

1.1.2. Diagnosis

CKD can be diagnosed by screening patients who have the possibility of developing kidney problems, such as patients with high blood pressure, diabetes, a family history of kidney disease, older age, particular ethnic group and smoking. (1) CKD can also be picked up when it leads to one of its recognised complications, such as cardiovascular disease, anaemia, or bone disease. Alternatively, it can be silent and be detected in a blood sample taken for another reason.

Creatinine is a waste product of muscle that can be measured by a blood test and used with data on age, gender and race to assess kidney function – estimated glomerular filtration rate (eGFR). The eGFR is a good measure of the degree of kidney function and necessary to determine the stage of kidney disease. The Modification of Diet in Renal Disease (MDRD) equation is used to calculate eGFR and has been the most widely used method to determine the level of kidney function, as it has proved the most robust and precise. (2) Although the National Institute of Health and Care Excellence (NICE) now recommend the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation to determine the level of kidney function. (3, 4) Normal GFR is approximately 100 ml/min/1.73m² and has an inverse relationship with creatinine (greater the creatinine, the lower the GFR). Creatinine levels may be in the normal range or appear normal in the early stages of CKD.

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CKD may also be discovered by testing a urine sample (urinalysis) where this shows that the kidney is losing protein or red blood cells into the urine. Various forms of medical imaging, blood tests and sometimes a kidney biopsy (removing a small sample of kidney tissue) are used to establish the cause and whether a reversible cause for the kidney dysfunction is present.

1.1.3. Classification

In February 2002, the National Kidney Foundation (NKF) in the USA published its Kidney Disease Outcomes Quality Initiative (KDOQI) Clinical Practice Guidelines containing the current definition of CKD. (5) This document:

1. Classified CKD into five stages according to renal function.
2. Suggested a standardised method of measuring and estimating renal function.
3. Described the rate of associated complications within each stage of CKD.
4. Suggested guidelines for the subsequent management of this disease.

The stages range from stage 1 with normal function ($\text{eGFR} \geq 90 \text{ ml/min/1.73 m}^2$) to stage 5 with severely impaired function ($\text{eGFR} \leq 15 \text{ ml/min/1.73 m}^2$). Subjects with $\text{eGFR} \leq 60 \text{ mL/min/1.73 m}^2$ for \geq three months are classified as having CKD. (1) These guidelines have now been adopted and adapted worldwide. In the UK, the Royal College of Physicians (RCP) published the “Chronic Kidney Disease in Adults- UK guidelines for identification, management and referral” in March 2006 (6), and following this the National Institute for Health and Clinical Excellence (NICE) published the CKD guidelines in May 2008 (7).

The spectrum of this condition ranges from stage 1, the mildest and usually causing few to no symptoms, to stage 5 the most severe requiring RRT with poor

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life expectancy if untreated. Guidelines published by Kidney Disease: Improving Global Outcomes (KDIGO) have reclassified CKD taking into account not only glomerular filtration rate as in the KDOQI guidelines (G1, G2, G3a, G3b, G4 and G5) but also the level of albuminuria (A1, A2, A3).(8) The KDIGO classification of CKD and Albuminuria are described in Table 1.1:

Table 1.1: Kidney Disease Improving Global Outcomes (KDIGO) stages of Chronic Kidney Disease and Albuminuria

Stage	GFR (ml/min/1.73m ²)	Description
1	90 ⁺	Normal or high
2	60-89	Mildly decreased
G3a	45-59	Mildly to moderately decreased
G3b	30-44	Moderately to severely decreased
G4	15-29	Severely decreased.
G5	<15	Kidney failure
Stage	Albuminuria (mg/mmol)	Description
A1	<3	Normal to mildly increased
A2	3-30	Moderately increased
A3	>30	Severely increased

1.1.4. Causes

Diabetes and hypertension are the most common causes of CKD that lead to kidney failure. (9) Diabetes and high blood pressure may also speed up the progression of CKD in someone who already has the disease. Some of the other causes of CKD include(8):

- a. Kidney diseases such as glomerulonephritis.

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- b. Kidney conditions that cause infections such as reflux nephropathy and pyelonephritis.
- c. Inherited kidney conditions such as polycystic kidney disease.
- d. A vascular disease which causes narrowing of the renal artery which carries blood to the kidneys,
- e. Drugs such as nonsteroidal anti-inflammatory drugs (NSAIDs) and certain antibiotics.

1.1.5. Prognosis

CKD is a significant global public health problem (10) affecting 10–16% of the adult population in Asia, Australia, Europe, and the United States of America (USA). (11) An estimated 0.2% of the population (125,000 individuals in the UK approximately) have stage 5 CKD. (12) At this level of function, the patients develop symptoms and complications and might need to start RRT (dialysis or kidney transplantation). Each year in the UK almost 8,000 patients commence RRT, half of whom are over 65 years of age (13). The presence of CKD also markedly increases the risk of heart disease which is significant despite taking into consideration the traditional risk factors such as hypertension and diabetes mellitus. (14) Cardiovascular disease is the most common cause of death in patients with CKD. (15) Research has shown that overall mortality increases as kidney function decreases. (16) A systematic review conducted by Tonelli et al. has shown that unadjusted relative risk for mortality in participants with reduced kidney function compared with those without ranged from 0.94 to 5.0 and was significantly more than 1.0 in 93% of cohorts. (17) The research implications of increased mortality in CKD patients are discussed in detail in section 1.1.11.1.

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1.1.6 Chronic kidney disease in the elderly

Over the next two decades, it is anticipated that the number of people aged over 65 will increase by 51% in the UK(18). CKD is an independent risk factor for cardiovascular mortality in patients with diabetes, hypertension, heart disease, and stroke, all of which are significant co-morbidities in the elderly. (19) Elderly patients are more likely to have CKD. Also, with growing life expectancy, patients are living longer with chronic conditions such as CKD (20, 21). The last decade has seen an increasing number of elderly patients referred to nephrology with CKD. (22) Although over the last decade, as a result of the steady growth in renal services in the United Kingdom, the incidence rates of RRT had plateaued, the recent UK Renal Registry Report shows that there has been an increase in the recent years. (23) The improvements in patient survival have led to an increase in the prevalence rates of RRT.(24)

1.1.7. Epidemiology

1.1.7.1 Prevalence of chronic kidney disease

The introduction of eGFR reporting and consequent adoption of a five-stage CKD definition based on GFR has resulted in the detection of a significant number of people with previously undiagnosed CKD. (25) The estimated prevalence of CKD ranges from 2.5% to 7.2% (26-31) with the prevalence in the elderly significantly higher at 35% (32). Table 1.1 gives a summary of population-based studies that reported the prevalence of CKD defined by $eGFR \leq 60 \text{ mL/min/1.73 m}^2$ using the MDRD equation.

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1.1.7.2 The incidence of chronic kidney disease

There are only a few studies reporting the incidence of new-onset CKD. In a population-based retrospective cohort study from the UK with 5.5 years of follow-up, the estimated annual incidence of CKD (defined as serum creatinine ≥ 150 micromol/L for six months or longer) was 1700 per million population. (33) In the Framingham Offspring study which consisted of 1223 men and 1362 women who had no pre-existing kidney disease, after a mean follow-up of 18.5 years, 244 participants (9.4 per cent) had developed CKD (defined as MDRD eGFR of <60 mL/min/1.73 m²). (34)

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Author (ref.) Year	Country	Study Population	CKD stages	Chronicity criterion	Albuminuria	Prevalence of CKD
Coresh et al. (30) 2005	US	3 rd National Health and Nutrition Examination Survey (NHANES III, 1999–2000)	3-5	No	Yes	3.8%
Hemmelgarn et al. (32) 2006	Canada	A community-based cohort of elderly subjects (\geq 66 years) in Calgary Health Region	3-5	Yes	No	35.5%
de Lusignan et al. (35) 2005	UK	Twelve General practices in UK	3-5	No	No	4.9%
Hallan et al. (29) 2006	Norway	Health Survey of Nord-Trondelag County (HUNT II) study	3-4	No	Yes	4.7%
Viktorsdottir et al. (28) 2005	Iceland	Reykjavik Heart Study	3-5	No	No	7.2%
Chen et al. (27) 2005	China	The International Collaborative Study of Cardiovascular Disease in ASIA (InterASIA)	3-5	No	No	2.5%
Shankar et al. 2006	Singapore	Private census study	3-5	No	No	6.6%

Table 1.2: Prevalence of Chronic Kidney disease in population-based studies using the Modification of Diet in Renal Disease (MDRD)

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1.1.8. Referral to Nephrologist

Guidelines for referral to a nephrologist can be different between countries. In the UK, NICE CKD guidelines suggest referral of patients with: (4)

- a. eGFR ≤ 30 ml/min/1.73 m², with or without diabetes;
- b. Proteinuria (albumin creatinine ratio-ACR) of 70 mg/mmol or more, unless known to be caused by diabetes and already appropriately treated.
- c. ACR 30 mg/mmol or more, together with haematuria.

The NICE guidelines have been modelled based on the recommendations made in the KDIGO 2012 clinical practice guidelines for the evaluation and management of CKD. The current referral practice in the UK from general practice to Nephrologist is summarised below (4):

- a. By stage 4 CKD (when eGFR is less than 30 ml/min/1.73m²)
- b. eGFR decreasing by more than 3 ml/min/1.73m²/year
- c. At an earlier stage (e.g. CKD3) when urine albumin-creatinine ratio (ACR) is more than 30 mg/mmol.
- d. When blood pressure is difficult to control
- e. When there is haematuria, or other findings suggest a primary glomerular disorder or secondary disease amenable to specific treatment.

1.1.9. Unreferred CKD

Only a few studies look at the burden of unreferred CKD. A study in the UK by John et al. showed that the median age of the unreferred population (eGFR ≤ 30 mL/min/1.73 m²) was 80 years (range, 18 to 102 years), 53.6% were men,

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median GFR was 26.3 mL/min/1.73 m² (range, 3.6 to 42.3 mL/min/1.73 m²) and 39.5% of the patients had died over a mean follow-up of 31.3 months. (36) Even in advanced CKD, only 35% to 50% of patients are referred, although this may be appropriate because of age and comorbidity. (37, 38) In comparison to unreferred patients, those under the care of nephrology have not only more advanced CKD but also increased comorbidity. (36, 39-42) There is very sparse evidence regarding the outcomes associated with unreferred CKD in the medical literature. Studies have shown that newly referred, or unreferred elderly patients with CKD are more likely to die before reaching ESRD. (43-45)

1.1.10. Implications of guidelines

KDOQI Clinical Practice Guidelines for CKD: Evaluation, Classification, and Stratification were published in 2002, and over the fifteen years the changes in clinical practice, research, and public health as a result of this guideline have been substantial. (5, 46). As a consequence of these guidelines, a significant number of patients with CKD have been detected.

1.1.10.1. Policy in the UK

The Renal National Service Framework (NSF) published in 2004 and set out the targets for the care of people with kidney disease, and guidance to help healthcare providers detect the condition at an early stage and slow down its progression (47, 48). The NSF (Part 2) discussed prevention and early recognition of CKD and suggested that laboratories should report a formula-based estimation of GFR on blood tests taken for serum creatinine measurement in adults. (25) In April 2006 the Department of Health introduced mandatory eGFR reporting in England using the MDRD study equation for all laboratories. Simultaneously, the General

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Medical Services Contract's Quality and Outcomes Framework (QOF) introduced a register of people in primary care with CKD. The QOF is mostly an 'annual reward and incentive programme detailing general practice achievement results, intended to benefit both patients and the National Health Service (NHS). (49) The QOF offers financial incentives for the detection and treatment of CKD and hypertension in primary care. Since its introduction, the UK has observed a definite reduction in numbers of 'late-presenters', defined as patients presenting to renal services within 90 days of needing RRT, from 31% to 19% in the past few years. (50)

1.1.10.2. Financial Implications

The financial consequences of CKD are substantial. Around 1.3% of the NHS funding (£1.45 billion) is spent on CKD, with over half of this expenditure for RRT. Also, cardiovascular complication management of CKD is a significant portion (51). These figures are similar in Australia where CKD- and RRT-associated costs are estimated to increase by 37% from \$1.3 billion in 2012 to \$1.7 billion in 2020 (1 Australian \$ = 0.55 British £, 31st March 2018; Australian population 24m vs English population 53m). (52) Given the substantial burden of the disease on people and the financial implications of CKD, it is imperative that large-scale generalisable studies in CKD are conducted.

1.1.11. Impact on Quality and Quantity of Research in CKD

Studies that will lead to better treatments and cures for CKD are essential. Since the publication of the KDOQI CKD guidelines, there has been a significant rise in the number of studies exploring the various stages of kidney disease. An editorial by Coresh et al. stated that the number of articles in the SCOPUS database related to CKD research had increased from 188 in the year 2000 to 356 in the year 2002

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and 4,035 in the year 2011. These CKD-related articles comprised 0.7%, 1.6%, and 11.2% of all nephrology research publications in the years 2000, 2002 and 2011 respectively. (53) Considerable efforts are being made and resources allocated to find new treatments for CKD or treatments to slow progression. Unfortunately, CKD research has been a challenge, and these issues that have been outlined in section 1.1.11.1 below have contributed to the failure to translate research into public health practice. (54, 55)

1.1.11.1. Challenges of CKD Research

As previously discussed in section 1.1.5, patients with CKD are likely to have an increased comorbidity burden and mortality. (17, 56) Patients with CKD are likely to have minimal symptoms until it reaches late stages and therefore testing treatments to slow the progression of CKD have been challenging. Patients with CKD are also likely to be frailer and of lower educational status compared to the general population. (56) In America, a survey conducted between 1999-2008 showed that 26.7% of adults with CKD had high school education which was just below the national average of 28.4%. (56) Both language and illiteracy can lead to a lack of understanding of research studies, including their purposes and materials (56). The audit also showed that the percentage of adults with CKD in America that are disabled was estimated to be 18.3% in comparison with 9.9% in the general population, (56) and these people will be more dependent on other members of the family to help them attend hospital appointments. The majority of CKD patients are burdened with polypharmacy, and by the time they reach stage 5 CKD, it is predicted that the typical patient will take 10-12 medications. (57) In addition to increasing medications, participating in research increases the

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number of visits to the hospital for CKD patients, which may serve as another deterrent to participating in clinical research.

All of the above issues in patients with CKD pose a barrier to research in CKD patients, and they are often excluded from research trials or refuse to participate.(55, 58) These obstacles, in turn, have significant implications upon the generalisability of CKD research as the recruited participants are not representative of CKD patients in the general population. The consequence of the lack of generalisability of research findings of CKD management has added to the challenge of translating research into public health practice. (54, 59) There is, therefore, perhaps, a particular need to address study design when undertaking research to improve the delivery of care to patients with kidney disease (60).

1.2 *Clinical study designs*

With the problem of CKD increasing, research regarding the management and treatment of CKD, to improve morbidity and mortality associated with CKD is vital. Well-designed studies are of utmost importance to enhance the care we deliver to patients with kidney disease (60).

1.2.1 The Evidence Pyramid

Study designs regularly used in nephrology research are observational studies, like cohort and case-control studies, and interventional studies like randomised controlled trials (RCTs) (61). Figure 1.1 depicts the evidence pyramid which can be used to understand the certainty of medical evidence. Typically, studies of cause and prognosis utilise cohort designs, whereas studies of therapy frequently

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utilise the clinical trial designs. However, observational study designs using causal models can also be used to test the treatment effect.

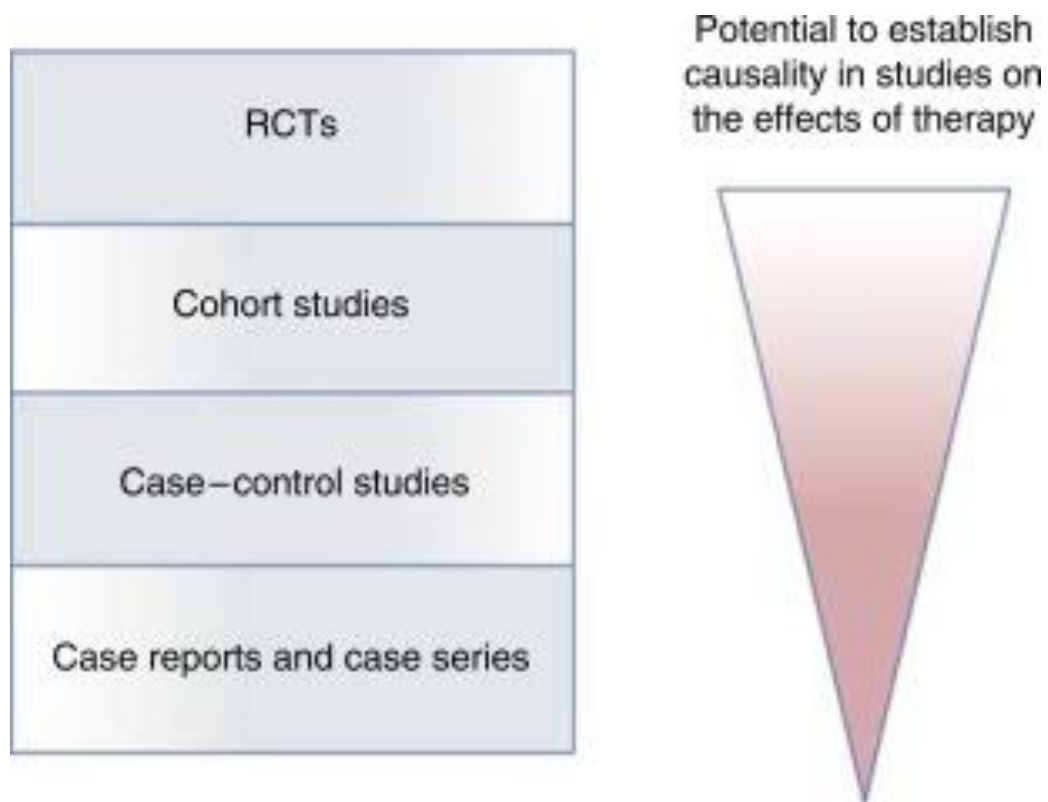


Figure 1.1: Evidence Pyramid (adapted from “The valuable contribution of observational studies to nephrology(62)”

1.2.2 Randomised Control Trials

RCTs are considered to represent the gold standard for testing hypotheses in medical research. (63) In an RCT, the critical requirement is that the patients are randomly assigned to the experimental group (with exposure) or the control group (without exposure) by a pure chance process. The randomisation helps to prevent selection by the clinician and helps to establish groups that are equal on relevant prognostic factors. It should be noted that randomisation does not guarantee to make all else equal for measured and unmeasured variables; it ensures that any differences occur by chance. Studies may be single-blind (either the patient or the clinician does not know who receives the treatment and who does not) or double-

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blind (both the patient and the clinician do not know who receives the treatment). In contrast, in open-label RCTs both the researchers and participants know which treatment is being administered, an approach which tends to be used for comparing two very similar treatments to determine which is most effective. One reason for 'blinding' is that the patient, as well as the clinician, may act contrarily if they know about treatment allocation. A distinct advantage of RCTs over observational studies is that they can provide evidence for a causal relationship because they have the potential to overcome some forms of selection bias. The two groups are followed up for a specified period or until a required number of events have occurred and then compared regarding the outcome.

1.2.2.1 Randomised Control Trials in Nephrology

A recently published systematic review identified that only 1,054 (2.6%) of 40,970 trials overall, were attributed to nephrology. (64) Between the various medical specialities, Nephrology had published fewer RCTs with regards to both number and quality. (65) A common concern in nephrology is the lack of RCTs, and thus the failure to decisively establish a cause-and-effect relationship between exposure and an outcome. A large proportion of these RCTs in Nephrology have also had null findings(66, 67). Research also suggests that the quality of RCTs within nephrology are suboptimal and that the reporting of results in these RCTs is of low quality. (65, 68-72) There has been a lack of decent quality RCTs investigating appropriate screening and monitoring in the early stage of CKD. (73) A systematic review has determined that evidence on outcomes in patients with CKD have been limited, as they have frequently been obtained from post hoc analyses of patient subgroups enrolled in RCTs. Negative results from several recent large

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RCTs have led to a guarded attitude towards designing and conducting RCTs.(74-81)

Studies involving patients with CKD, in the past, have produced negative results probably as a result of methodological flaws in study design. (82) The absence of an agreement regarding the endpoints in Nephrology (doubling of creatinine, a decline of eGFR > 25%, requiring dialysis.) have resulted in contradictory results in Nephrology RCTs. (83) Also, studies in Nephrology have commonly been underpowered due to overeager speculation about event rates and the outcome of therapeutic interventions. These issues must be well-thought-out when planning RCTs. Good quality, meticulously conducted pilot studies are necessary before the design of large adequately powered hard-endpoint clinical trials (84). These issues have resulted in some professional guidelines concluding that no firm recommendations can be made about the efficacy of many therapeutic interventions. (85) As a consequence of the issues highlighted above and in the current economic climate, there is a particular role for well-conducted observational cohort studies to inform clinical practice in nephrology. (86)

1.2.3 Observational studies

Most of the medical research is observational with nine out of ten research papers published in clinical speciality journals describing observational research (87, 88).

The types of observational study designs are:

1. Case report or case series: This describes the clinical course of individuals with a particular condition or diagnosis.
2. Case-control studies: This design begins firstly by identifying participants with (cases) and without the condition of interest (controls). The exposure of interest is determined retrospectively and compared between cases and

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controls. Exposures that are more common in cases may give clues to causal relationships, provided that cases and controls were similar in all respects except for the condition of interest.

3. Cohort study designs: These are increasingly popular in nephrology and can be of a quasi-experimental design, combining the essentials of observational and interventional research methods. The group of people who have a standard feature are recruited and then observed in their natural setting as partaking or not having the intervention (or exposure), and outcomes are subsequently assessed. In summary, cohort studies, begin by identifying exposure amongst a group of people who are free of the outcome of interest and evaluating the participants for events of interest over time. (89) Cohort studies remain at the top of the ladder of observational studies and are invaluable in studying rare exposures, examining multiple potential effects of a single exposure, testing multiple hypotheses and capturing adverse effects/harm in the long term (89).

1.2.3.1 The scope of observational research

Although RCTs represent the gold standard for testing hypotheses in medical research, they are not a panacea, and there is a vital role for observational studies in understanding disease progression and treatment effectiveness. (90, 91) Also due to ethical or other concerns, RCTs may be problematic or impossible to conduct (62, 66, 92). Both observational studies and RCTs fulfil a harmonising and valuable role in nephrology. When rigorously conducted, cohort studies could potentially produce results that are similar to those from randomised controlled trials (RCTs). (67, 92) For example, an analysis of 18 randomised and observational studies in health services research found that treatment effects may

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differ based on the research design, but that “one method does not give a consistently greater effect than the other.”(93, 94) The treatment effects were most similar when the exclusion criteria were similar and when the prognostic factors were accounted for in observational studies(95).

Even if observational studies do not provide a definitive answer; they can be used in these settings to refine hypotheses for clinical trials or provide evidence of sufficient equipoise to persuade patients and clinicians that randomisation is appropriate. This is important as RCTs can answer only one pre-specified question and take many years to provide evidence. They also tend to exclude the real world population with the condition, and hence the results may not be generalisable.

An example of an observational cohort study which has informed clinical practice is the international, Dialysis Outcomes and Practice Patterns Study (DOPPS). This study had collected data from countries in five continents and used an instrumental variable approach to explore causal relationships between practice patterns and outcomes and influence dialysis practice. (96)

However, as with clinical trials, a significant challenge to observational research is external validity. One approach to deal with this is to collect information on the general population from which the study population is taken. For example, in the North American Atherosclerosis Risk in Communities (ARIC) study, external validity (generalisability) was examined by nesting study patients in communities covered by broad surveillance. In the community surveillance component, the occurrence of myocardial infarction and coronary heart disease death was ascertained for all residents of the communities. (97, 98) The events were investigated by review of hospital records and by query of physicians. This helped

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to understand the representativeness of the study participants to the broader community.

1.3 Validity of research

It is more than 50 years since Campbell and Stanley published one of the first influential papers to raise concerns about threats to validity in research (99, 100).

Validity can be assessed in two ways – internal validity and external validity.

1. Internal validity relates to the rigour of study design (how well intervention has been performed) and is the degree to which the results are attributable to an independent variable and not some rival explanation (X, the independent variable, causes Y, the dependent variable). The less chance for confounding in a study, the higher the internal validity.
2. External validity is the extent to which the results of a study can be generalised to other situations and other people - 'real world'.

Internal validity has tended to be considered of higher importance by many researchers than external validity. As a result, more attention has often been paid to enhance internal validity, with the notion that it is more vital to know if a treatment is effective in a study population, than to know if it will be useful in every context (e.g. country), setting (e.g. primary/ secondary/ tertiary care) and participant case mix (e.g. age, sex, ethnicity, comorbidity and socioeconomic status). (101, 102) At the same time funding bodies and journals have placed more emphasis on the methodical accuracy of studies (internal validity) than on the applicability of results (external validity). As a result, there has been a failure or delay in the translation of research findings into healthcare improvement(103, 104). This has been highlighted by Balas and Boren who found that it takes approximately 9.3 years to implement evidence of original research to the benefit

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of patient care(105). Therefore, researchers should pay adequate attention to external validity (generalisability) when designing a study. (106)

1.3.1 External Validity: Components

External validity is often used interchangeably with the term "generalisability".

(106) External validity can be divided into four components. (102)

1. Population: Population validity is the representativeness of the study population to the population as a whole, that is, whether the findings from the study sample can be generalised to the population as a whole.
2. Setting: This refers to the applicability of findings to other contexts, situations or locations. Quantitative research typically focuses on a single setting/context, or a small number of settings/contexts. To improve the external validity of a study, researchers are required to carry out the same experiment in diverse contexts. The researchers should consider conducting the experiment in different organisational types, countries, cultures, and so forth.
3. Across treatments: Both experimental and quasi-experimental research designs involve specific treatments. This component of generalisability refers to the characteristics of the intervention - features of the treatment or intervention have to be similar when applied to different populations or settings to arrive at the same conclusions.
4. Across time: This component refers to societal and temporal changes. It is useful for researchers to consider if the effect of the intervention will continue to apply as society changes over the years. For example, will a study conducted today still be useful ten years from now? Therefore, when making generalisations across time, caution must be exercised to evaluate whether the

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population, setting and treatments are still relevant or are likely to have changed over the period.

1.3.2 External validity: Threats

A range of potential threats to the external validity of various clinical study designs has been discussed in the literature. (107-111) These threats can arise either from the design, recruitment and conduct or the reporting stages of a study.

1.3.2.1 Threats at the design stage

When the participants in a study do not represent the population that the researcher hopes to make generalisations to, selection bias will result. As a result, it will be hard to generalise to the broader population from outcomes that have resulted from a biased sample. Studies that have either very selective eligibility criteria, with potential participants unrepresentative of patients in the local community, or have a single centre or geographic location from which participants are recruited, could have poor generalisability(107). Research is also often conducted with younger people, with fewer comorbid diseases, less medication, and who have low levels of frailty and cognitive impairment. The real world patients are often older, frailer, have multiple comorbidities and likely to die sooner (112, 113).

The extent to which the findings of a study can be generalised across populations (section 1.3.1) also depends on the range of the characteristics collected for the study sample. Frequently researchers strive to stratify the study population by the relevant socio-demographic variables, for example, so that there is a representative proportion of both sexes, people of different ages, and so on. However, other characteristics of the population are not accounted for such as

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qualifications, occupation, cultural, social and health service factors. This will limit the degree to which results can be generalised across populations.

The issues related to participant selection when designing the study are perhaps one of the most significant threats to external validity as the samples are not accurate representations of populations.

1.3.2.2 Other threats to external validity: retention

Recruitment into studies can frequently be challenging with older frailer patients and those with multiple co-morbidities less likely to agree to participate in studies (114). Non-participation can not only affect whether a study can answer the questions it is intended to (internal validity) but also the applicability of study conclusions to other people and situations (external validity). On the other hand, as discussed in section 1.3.1 the recruited participants frequently are different from those who are eligible but not recruited regarding age, sex, race, the graveness of disease, educational status, social class, and area of residence. (107) Selective attrition is also a known problem in research studies as those in disadvantaged socioeconomic groups, ethnic minority groups, younger and older participants and those at increased risk of poor health are more expected to drop out. (115) The loss to follow-up is also typical and occurs when, during the study period, participants drop out of the study. Differential loss to follow-up has a similar effect. Non-random dropout and loss to follow-up in studies again threaten the generalisability of results, as participants who complete the study may differ from people who drop out and as a result, the estimates of association are biased (116, 117).

1.3.2.3 Threats due to reporting

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Study reporting is as critical as the conduct of a study. Transparent reporting of studies is needed to better inform the reader on the issues of generalisability and selection bias(118). Imperfect and insufficient reporting of research impedes the evaluation of the merits and flaws of the research. Some studies fail to report on the applicability of the study data to a broader patient population. For example, although study reporting often includes the baseline clinical data of patients recruited into the study, so that clinicians can assess the applicability of the results to their patients, recorded baseline data do not include information on the actual composition of the study population (all patients who were eligible to participate in the study). This, therefore, is misleading, and the clinician is genuinely unable to make generalisations to the study population. It is therefore of importance for readers to know if results can be generalised to an individual patient or groups of patients that differ from those enrolled in the study with regard to age, sex, severity of disease, and comorbid conditions; and whether similar results can be expected at the primary, secondary, and tertiary levels of care. Figure 1.2 summarises threats to generalisability at the various stages of a study.

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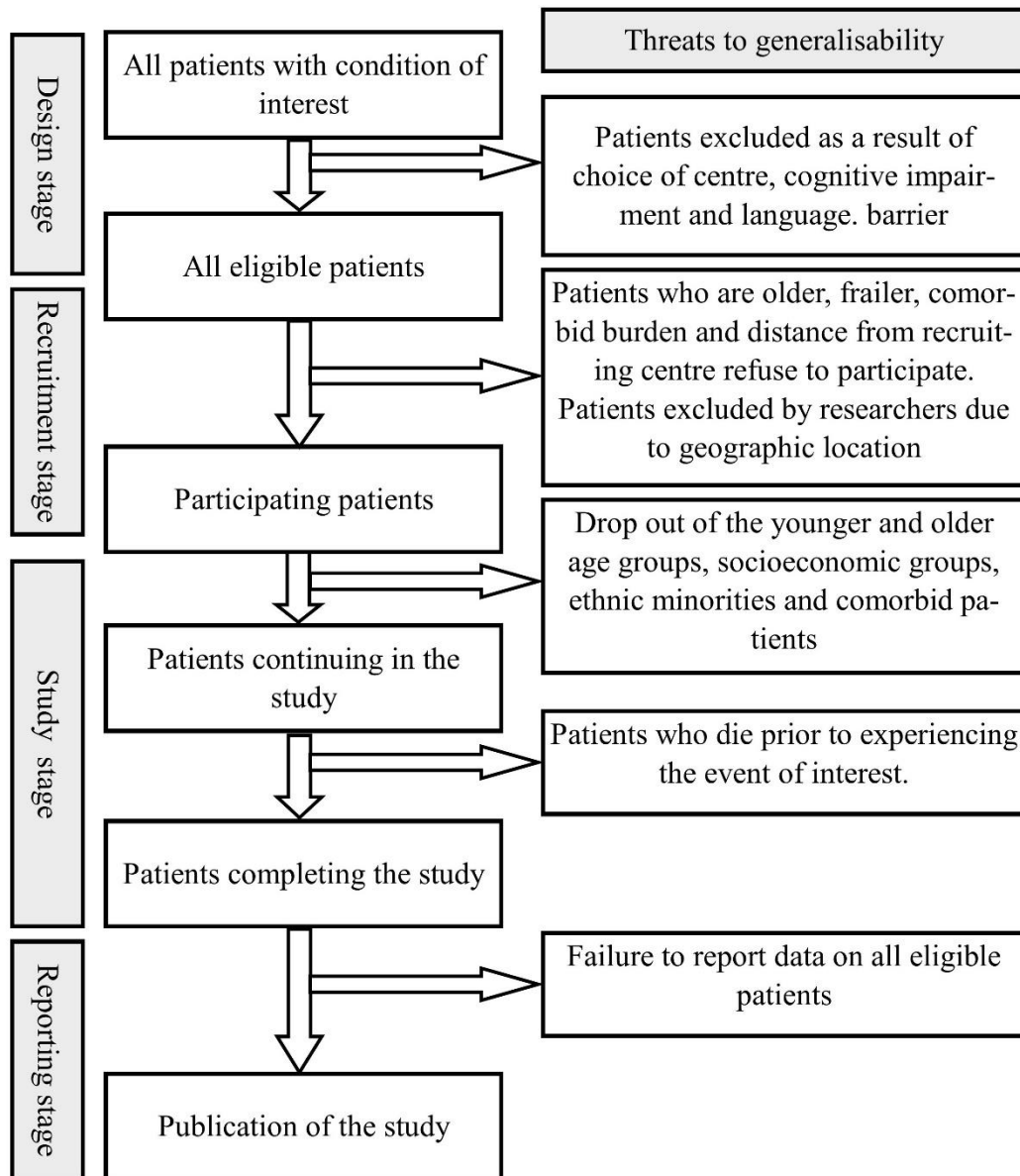


Figure 1.2: Threats to generalisability at various stage of the study.

1.3.3 Methods to improve external validity

Several authors have emphasised the importance of controlling for threats to external validity. (119-121) The generalisability of a study can be improved in several ways. (122) Researchers can enhance the generalisability of their conclusions by assessing the representativeness of the sample statistically at the design stage. Random selection of participants, although not always feasible,

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increases the generalisability of findings to the target population, and broad eligibility criteria improve the generalisability to other populations.

Merely addressing issues of sample selection does not improve external validity; other threats to external validity must also be addressed. Generalising beyond the sample of the study should be based on the size and representativeness of the sample, target population, analytic methods and setting. (123, 124)

Reporting of a study should be in sufficient detail to allow for replication of the study to determine if the same results are obtained in other circumstances. (125, 126) Also by openly acknowledging the limitations of their study, researchers assist readers in making informed decisions about generalising findings to new settings or populations. Researchers should be cautious in discussing the application of their findings from studies that have limited external validity. In many studies, small samples might impede generalisability of findings to other populations; however, integrating the findings with other similar research studies reported in the literature can be useful for positioning the study within the knowledge of the discipline. (123) In this way, smaller studies can contribute to the theory that can be applied and evaluated in other settings and populations.

In summary, there are four fundamental ways in which the results of interventional or observational studies can be made more broadly generalisable:

- (1) Optimum design and conduct at recruitment: By having broad inclusion criteria and efficient patient recruitment (achieving the sample size)
- (2) Careful follow up of all participants
- (3) Quantification of any selection effect during the recruitment process: by accurately recording patient recruitment (using screening logs), and drop out (127).

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(4) Detailed understanding of the setting in which research is performed: by describing any peculiarities of the health-care system in which the study took place. (125, 128)

1.4 Summary and scope of the thesis

This thesis began by describing the burden of CKD and the significant increase in research since the introduction of KDOQI CKD guidelines. The chapter highlighted the need for high-quality observational studies to contribute to the evidence base. However, external validity (generalisability) remains a pitfall of observational research. This Doctorate of Philosophy (PhD) adopts a methodological approach to understanding and enhancing the generalisability of observational studies. The PhD is embedded within the multi-national and multi-centre European Quality (EQUAL) Study on treatment in advanced CKD funded by the European Renal Association and European Dialysis and Transplantation Association (ERA-EDTA) for which Bristol is the national coordinating centre in the UK.(129)

The overarching aim of the thesis is to understand generalisability, and issues of recruitment in cohort studies: the example of advanced CKD in the elderly (EQUAL). The thesis consists of three broad objectives, using EQUAL as a case study:

1. To quantify selection biases occurring during the recruitment to the (observational) EQUAL study and their implications for generalisability.
2. To understand issues underpinning patient recruitment to the (observational) EQUAL study.

Chapter 1: Introduction

3. To determine if the quality of reporting of observational studies has improved after publication of the STrengthening the Reporting of OBServational studies in Epidemiology (STROBE) statement.

1.5 Structure of the Thesis

The introduction chapter will be followed by Chapter 2 which describes the context and design of this PhD study. It will outline the EQUAL study and types of mixed methods study design, and then detail the study design of the thesis.

The PhD is composed of three sub-studies, each addressing one of the above-stated objectives.

Chapter 3 (Objective 1) is dedicated to the first study of the thesis titled “Using primary care data to understand the generalisability of clinical cohorts: The example of advanced CKD in the elderly.” This chapter explores the threats to generalisability at the design stage of a cohort study by quantifying selection biases that occur during the recruitment to observational studies and explores how participants in a cohort study differ from the wider population of patients that they are intended to represent.

Chapter 4 (Objective 2) is a qualitative study titled “Understanding patients’ perspectives that could influence recruitment in kidney studies”. This chapter aims to determine the threats to generalisability at the recruitment stage of the study by teasing out issues that underpinned patient recruitment to the EQUAL study. Its goals are to understand the motivation for participation and any perceived barriers.

Chapter 5 (Objective 3) is a systematic review titled “Assessing the Design and Quality of Reporting of CKD Cohort Studies Assessing Mortality in the Elderly Before and After the publication of STROBE: A Systematic Review.” The chapter

Chapter 1: Introduction

aims to examine the threats to generalisability at the reporting stage of a cohort study.

The final chapter (chapter 6) of the thesis is a discussion chapter intending to bring together the main findings and conclusions of the thesis.

CHAPTER 2. METHODS: CONTEXT AND DESIGN

The previous chapter described the burden of Chronic Kidney Disease (CKD) and the growth of research in this field. The chapter also highlighted the limited number of adequately powered; high quality randomised controlled trials (RCTs) in nephrology to allow the establishment of causality (causal conclusions). The chapter made a case for good quality observational studies such that they can contribute more robustly to the evidence base. However, external validity (generalisability) remains a crucial Achilles heel of observational research. This Doctor of Philosophy (PhD) was designed to tease out the threats to generalisability in observational research by embedding within the multi-national and multi-centre European Quality (EQUAL) Study on treatment in advanced chronic kidney disease (CKD). This PhD is of a mixed methods design with three arms including a. Quantitative b. Qualitative c. A systematic review, aiming to explore the threats to external validity in the design, recruitment and reporting stage respectively. This chapter gives an overview of the EQUAL study, the role of mixed methods study designs and the advantage of using multi-methods to explore a research problem. The detailed methods relating to each of the three arms of the PhD thesis are contained in the relevant chapters.

2.1. EQUAL (European Quality Study on the treatment of advanced chronic kidney disease)

EQUAL is an international prospective cohort study funded by the European Renal Association, European Dialysis and Transplant Association (ERA-EDTA). (129), and was conceived about ten years ago when representatives of the European registries

Chapter 2: Methods

met to plan the establishment of a CKD register. The best alternative was decided to undertake an observational study looking mainly at the timing of the start of dialysis in elderly patients with advanced CKD with the purpose of focusing on both the quantity and quality of life.

2.1.1. Design

EQUAL was carried out in six European countries: Germany, Italy, Netherlands, Poland, Sweden and the United Kingdom. The initial plans were for the participants to be recruited over two years and followed for a maximum of four years.

2.1.2. Objectives

2.1.2.1 Primary Objectives

The primary objectives of EQUAL were to establish the level of kidney function (determined by blood results and physical signs or symptoms) at which overall quantity and quality of life would be optimised by starting Renal Replacement Therapy (RRT) in patients aged 65 years or over.

2.1.2.2 Secondary Objectives

1. To determine how uraemic signs and symptoms develop during the progression of advanced CKD.
2. To determine the optimal laboratory measure of kidney function in advanced CKD at which to start RRT (regarding optimising quantity and quality of life).
3. To determine the factors that influence nephrologists, patients and carers when deciding whether/ when to start RRT.
4. To determine whether patients are satisfied with decision making about whether/ when to start RRT.

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2.1.3. Selection of Subjects

2.1.3.1 Inclusion Criteria

1. Aged 65 years and over
2. Attending nephrology clinic with a first eGFR of 20 ml/min/1.73m² (or less if presenting late) within the last six months, regardless of subsequent eGFRs.

2.1.3.2 Exclusion Criteria

1. History of dialysis or kidney transplantation.
2. If the current decrease in eGFR is thought to be due to an acute event (Acute Kidney Injury-AKI) with eGFRs before this event not having been ≤ 30 ml/min/1.73m² for at least 3months.
3. Patients are unable to give informed consent or have communication problems (including limited English language).

2.1.3.3 Study sites

In the UK, Bristol (Southmead Hospital) was the national coordinating centre with 13 other sites used for recruitment. In England, Birmingham (Heartlands & Queen Elizabeth Hospital), Liverpool (Royal Liverpool Hospital), Manchester (Manchester Royal Infirmary), Oxford (Churchill Hospital), Salford (Salford Royal) and Stevenage (Lister Hospital) were the recruiting sites. In Scotland, Glasgow (Queen Elizabeth University Hospital) was the only recruiting site. In Northern Ireland, Antrim (Antrim Area Hospital), Belfast (Belfast City Hospital), Londonderry (Altnagelvin Area Hospital), Newry (Daisy Hill Hospital) and Ulster (Ulster Hospital) were the recruiting sites.

2.1.3.4 Selection of Participants

The potentially eligible patients were identified retrospectively from the clinical renal IT systems, ward lists and clinic lists. The patients were recruited within a

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six month +/- 6-week window from when they became eligible (first drop in eGFR ≤ 20 ml/min/1.73m²).

2.1.3.5 Patient invitation

Patients who met the inclusion criteria but not exclusion criteria were invited to take part in the EQUAL study. The patients were sent the patient invitation letter (PIL) (Appendix 2.1) along with the Pamphlet “An introduction for patients” (Appendix 2.2) and the patient information sheet (PIS) (Appendix 2.3). Unless the patient had contacted the department to decline participation in the study; the research nurse would contact the patient within two weeks to see if they would like to participate. If so, the initial study visit was arranged.

2.1.4. Duration of the study

The study would run for four years from the beginning of patient recruitment in a site. The start date would, therefore, define the end date of the study. As recruitment would take place over the first two years of the study, individual subjects would remain in the study for between two and four years. All sites in the UK closed for recruitment in 2015.

2.1.5. Study Procedures

2.1.5.1 Case record form

The case record form included details such as patient demographics and primary renal disease (PRD) of the patients according to ERA-EDTA PRD coding system; co-morbidity of patients; surgical history; dietary prescription, hospital admissions; medications and nutritional status evaluation.

2.1.5.2 Patient Questionnaire

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The patient questionnaire included lifestyle questionnaire, Quality of Life, SF-36 and kidney disease symptom questionnaire; Decision-making, questions about the information given to the patients and preferences of patients about treatment; Patient satisfaction, Renal Treatment Satisfaction Questionnaire (RTSQ) and Brief Illness Perception Questionnaire.

2.1.6 Follow-up

The follow-up in EQUAL was designed such that it would coincide with the patient's routine clinic visit. The follow up would be every six months until the eGFR was ≤ 10 ml/min/1.73m². It would then be at three monthly intervals until the end of follow-up, or the participant had been on dialysis for six months (when follow-up returns to six monthly). Study visits were performed at +/- six weeks of the protocol date except for the start of dialysis visit which would need to occur within the six weeks leading up to the start of dialysis or within the two weeks following the start of dialysis. Patients would be followed until death, renal transplantation, discharge from the nephrology clinic to primary care or until the end of the study.

2.2. *Mixed Methods design*

Historically, quantitative study designs have dominated health services research. However, over the past few decades, qualitative methods have been increasingly used by the health research community, with a rise in the publication of qualitative studies. (130, 131) As the role of qualitative approaches has been progressively acknowledged, there has been a growing interest in combining qualitative and quantitative methods. An article by O'Cathain et al. has shown that within

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England there was an increase in the percentage of studies classified as mixed methods from 17% in the mid-1990s to 30% in the early 2000s.(132)

2.2.1 Definition

Mixed methods research is a more specific form of multimethod research which includes a mixing of quantitative and qualitative methodologies to address a research problem. (133-135)

2.2.2 Reasons for using mixed methods design

Creswell lists the reasons and situations where a mixed method approach may be more appropriate. (136)

1. When both quantitative and qualitative data, help to provide a better understanding of the research problem than either type by itself. A solitary approach to understanding a problem is often misleading, so approaching a subject from different perspectives or archetypes may help to gain a holistic perspective.
2. Different methodologies offer unique strengths, using more than one helps to get a clearer picture of the social world and make an adequate explanation. The use of multiple methods enhances construct validity (a form of methodological triangulation). Mixed methods are now routinely advocated by methodologists. Therefore, mixing or integrating research strategies (qualitative and/or quantitative) in any and all research where undertaken is considered a standard feature of well-conducted research.
3. Multi-methodology is associated with pragmatism and practicality. This approach is likely to result in multiple viewpoints; biased and unbiased;

Chapter 2: Methods

subjective and objective and therefore likely to significantly enhance the validity of the research.

2.2.3 Mixed method study: Types

Creswell et al. noted that there were nearly forty different types of mixed methods studies in the literature. (137) These can be further reclassified into three broad categories as detailed by Johnson, Onwuegbuzie, & Turner et al., predominantly quantitative, predominantly qualitative and equal status designs. (138)

2.2.3.1 Predominantly Quantitative

In this approach, the research study is predominantly quantitative with qualitative methods added to supplement the study. For example, Prakash et al. aimed to evaluate the association between neighbourhood socioeconomic status and barriers to peritoneal dialysis eligibility and choice. (139) Multivariable models were carried out to describe the relationship between socioeconomic status and the likelihood of peritoneal dialysis eligibility and choice in a prospective clinical database of End Stage Renal Disease (ESRD) patients (Quantitative aspect). A constant comparative approach was used to explore patient-reported barriers to peritoneal dialysis eligibility (Qualitative aspect). This study showed that peritoneal dialysis eligibility and choice were not associated with socioeconomic status. However, socioeconomic status could influence specific barriers to peritoneal dialysis choice.

2.2.3.2 Predominantly Qualitative

In this approach, the research study is predominantly qualitative at its core with quantitative data added to enhance the study.

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DePasquale et al. performed a mixed methods study of Americans of North African descent and Caucasians of American descent, with CKD and their families with mainly qualitative structured group interviews to explore their views regarding information that is essential in educational material regarding RRT selection decisions. (140) The quantitative element involved each participant choosing the three most important features of treatment they thought other patients or families confronted with decisions about treatment of kidney disease, should contemplate from an itemised list of 36 factors. The study identified similar views from Americans of North African descent and Caucasians of American descent participants with patients identifying morbidity or mortality, autonomy, treatment delivery, and symptoms as essential factors. Family members, also, quoted effects of RRT decisions on patients' psychological well-being and finances as relevant information.

2.2.3.3 Equal status designs

In this approach, the research study equally integrates quantitative and qualitative methodologies. For example, a mixed methods study by Sattoe et al. aimed to explore the result of a specific form of peer-to-peer support on the self-management of patients aged 16–25 years with end-stage renal disease (ESRD). (141) These young patients had taken part in Camp COOL (CC), a programme that aims to aid young Dutch patients with ESRD gain self-management skills. The qualitative aspect involved semi-structured interviews with the staff, participants, and healthcare professionals. The quantitative aspect involved pre and post surveys among participants (n = 62) and observations during two camp weeks. The participants reported increased self-confidence, more knowledge of their kidney condition, and felt more responsible in managing their kidney

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disease. The survey showed all participants scored reasonably well on self-efficacy measures and health-related quality of life after CC. The results of both the quantitative and qualitative arm were complimentary.

2.2.4 Mixed method study: Designs

Hanson, Creswell and Plano et al. described six different mixed methods study designs. (142) Creswell and Plano in their subsequent publication narrowed the study designs to four major types. (143)

2.2.4.1 The Convergent Parallel (triangulation) Design

The Convergent Parallel Design is the most common and well-known approach and is also known as the triangulation design (Figure 2.1). In this design, the researcher collects quantitative and qualitative data concurrently followed by analysis of the two datasets separately. The integration happens by merging the results during interpretation (and sometimes during data analysis). The convergent design aids a complete understanding of the two databases and corroborates results from the different methods. This study design is also known as concurrent triangulation design; quantitative and qualitative data are collected and analysed at the same time. Data analysis is usually separate, and integration usually occurs at the data interpretation stage. At the point of interface one tries to look for convergence, divergence, contradictions, or relationships of two sources of data.

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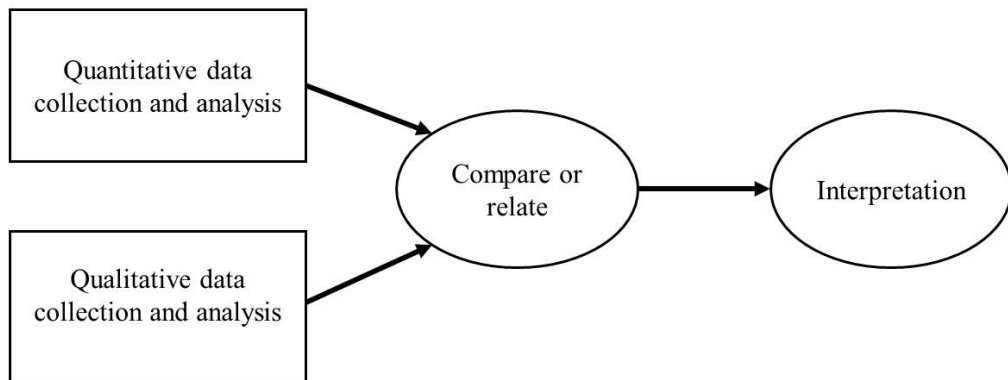


Figure 2.1: Convergent Parallel Design. Adapted from *Designing and Conducting Mixed Methods Research*. Creswell JW & Plano Clark (2007).

For example, Artsanthia et al. aimed to explore the palliative care needs of people living in Thailand with ESRD using a mixed method approach. (144) The qualitative arm of the study involved focus groups and interviews with patients and family members and adopted a thematic analysis approach. The quantitative aspect of the study used the Edmonton Symptom Assessment Scale which furnished descriptive data on nine symptoms commonly experienced by palliative care patients. The integration point was during the discussion phase. The themes discussed were supported by the results of the quantitative survey. The findings informed the development of a future intervention study.

Schmid-Mohler et al. intended to explore the presence of self-management tasks mastered by patients in the early phase after a kidney transplant. (145) To address this research question, a mixed method study design using semi-structured interviews (qualitative) to explore the perception of self-management tasks in kidney transplant recipients and a structured

Chapter 2: Methods

questionnaire (quantitative) to evaluate the existence or absence of 44 self-management tasks that had been identified in previously published reports was carried out. The qualitative interviews suggested that the patients found it difficult to manage the unpredictability in the early phase of the transplant and also to manage emotions such as uncertainty, disappointment, and frustration. The survey showed that in 50%, of patients, managing stressful emotions and self-perception was the most significant challenge.

The strong point of this design is that it is intuitive, efficient and lends itself to teams. The limitations of this design are that it requires substantial effort and expertise for the researcher or research team. There could be issues due to having different samples and different sample sizes when merging two data sets. In the analysis stage, there could be difficulty converging two sets of different data along with the issues of explaining discrepant results should they occur.

2.2.4.2 The Explanatory Sequential Design

In this design, the researcher starts by collecting and analysing quantitative data and as a follow-up to these results collects and analyses qualitative data in a second phase (Figure 2.2). The researcher connects the phases by using the quantitative results to shape the qualitative research questions, sampling, and data collection. The purpose of this design is to explain quantitative results (significant, nonsignificant, outliers or surprising results); qualitative results are needed to explain the findings. This design can potentially guide researchers to select the different patient groups to sample and interview based on quantitative results. This design is ideal where participants are available for the second wave of data collection; there is adequate time to conduct two phases, and the

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researcher/research team have limited resources and need to collect and analyse one data type at a time.

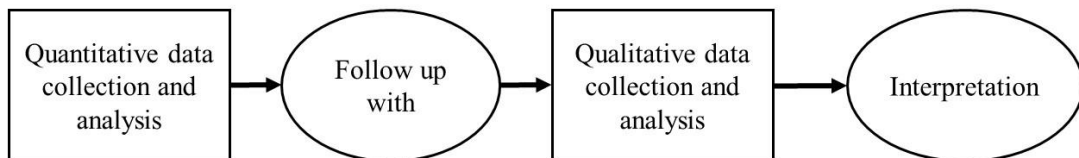


Figure 2.2: Explanatory Sequential Design. Adapted from *Designing and Conducting Mixed Methods Research*. Creswell JW & Plano Clark (2007).

Morton et al. in their mixed methods study intended to discover the essential factors of dialysis that influence patients and caregivers make decisions about treatment. (146). In the quantitative arm, using a nominal group technique, a rank of the most critical factors of dialysis on which patients and caregivers make decisions about treatment was obtained. Purposive sampling was then used to recruit participants into each nominal group. Integration of the two aspects of the study occurred following analysis of both phases. This approach helped to understand factors important to patients and caregivers about dialysis (treatment that enhances survival and can be performed at home).

Tong et al. aimed to determine patient preferences for how kidneys should be allocated for transplantation. (147) Patients on dialysis and renal transplant were purposively selected from two centres in Australia to participate in nominal/focus groups (Qualitative). Participants then identified and ranked criteria they

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considered essential for deceased donor kidney allocation (Quantitative). Most patients prioritised that matching, wait-list time, medical urgency, the likelihood of surviving surgery, age, comorbidities, duration of illness, quality of life, the number of organs needed and impact on the recipient's life circumstances were important considerations. Supporting their rankings were four central themes: enhancing life, medical priority, recipient valuation, and deservingness.

The limitations of this design type are that it may be challenging to obtain ethics approval when the second phase cannot be specified before the first phase complete. Although this design helps to theoretically inform patient selection to sample for the qualitative study in the different patient groups, it could equally create a dilemma regarding whom to sample and criteria to be used for sample selection for a qualitative study. For example, in both the above-listed studies had there been an extensive list of factors listed regarding dialysis by patients and caregivers or criteria essential for deceased donor kidney allocation would have caused a dilemma on whom to sample for the qualitative study. Also, the two phases require adequate time to implement, and the participants need to be contacted for the second round of data collection.

2.2.4.3 The Exploratory Sequential Design

In this design, the researcher starts by collecting and analysing qualitative data first.

This is also referred to as instrument development design. The purpose of this design is to generalise qualitative findings to a more substantial sample. The results of the qualitative data are used to build the subsequent quantitative phase. The phases are connected by using the qualitative results to shape the quantitative phase by specifying research questions and variables, and / or developing an

Chapter 2: Methods

instrument. (Figure 2.3) This design is useful where important variables are unknown, instruments are unavailable, or if new questions are likely to emerge from qualitative results.

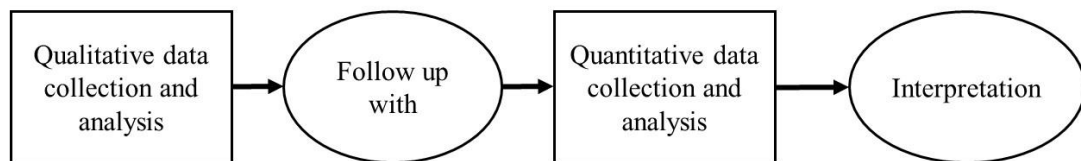


Figure 2.3: Exploratory Sequential Design. Adapted from *Designing and Conducting Mixed Methods Research*. Creswell JW & Plano Clark (2007).

Tam-Tham et al. conducted a mixed methods study to identify barriers and facilitators to conservative care for older adults with chronic kidney disease. (148), using an exploratory sequential design. First, they interviewed primary care physicians to determine their perspectives on conservative care for older adults with stage 5 CKD. They then designed a questionnaire based on the findings from the qualitative interviews to be used in a broader survey of primary care physicians to determine the prevalence of key barriers and facilitators to the provision of conservative care for older adults with stage 5 CKD.

Pai et al. used a sequential mixed-method design to explore strategies used by families to manage the post-transplant oral medication regimen in adolescents

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with renal transplants. (149) The qualitative arm involved semi-structured interviews assessing tasks used by family members. The qualitative arm informed the quantitative arm which involved assessment of pillbox filling, calling for refills and verifying that the pillbox was filled correctly. The integration of the two arms occurred following analysis of both phases. The study highlighted the need to bolster self-management skills among adolescents with renal transplants.

Similar to the explanatory sequential design one should have adequate time to conduct two phases as the researcher need to collect and analyse one data type at a time. However, the participants in the quantitative study might not all be the same individuals who provided qualitative data. The limitations are again similar to explanatory sequential design with two phases requiring adequate time to implement and difficulty applying for ethical approval as a result of an inability to specify quantitative procedures.

2.2.4.4 The Concurrent Embedded Design

In this design, the researcher collects and examines qualitative data within a quantitative research design or vice versa. The collection and analysis of the secondary data set occur before, during, and / or after the primary methods. (Figure 2.4). This study design is usually carried out to augment a research project, for example, to improve recruitment procedures in a study, examining the intervention process or explaining reactions to participation.

Chapter 2: Methods

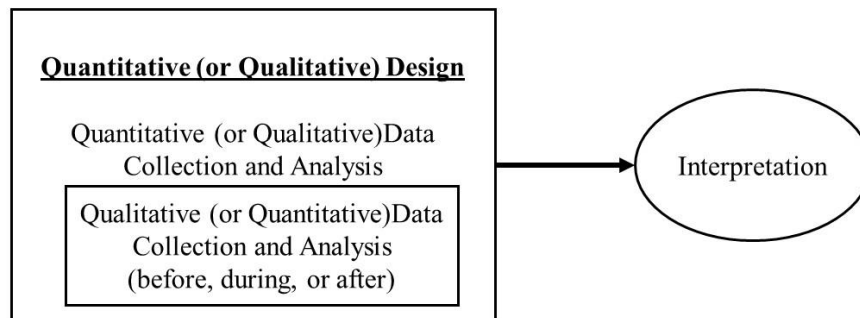


Figure 2.4: Concurrent Embedded Design. Adapted from *Designing and Conducting Mixed Methods Research*. Creswell JW & Plano Clark (2007).

To explore the palliative care needs of patients with a non-cancer diagnosis (end-stage heart failure, renal failure or respiratory disease), Fitzsimons et al. adopted a mixed method approach. (150) The quantitative aspect of the study used the SF36 Quality of Life survey and Hospital Anxiety and Depression questionnaire. The qualitative arm involved nested interviews and focus groups. Results were reported separately with minimal integration during the analysis phase with the conclusion that patients dying from chronic illness in this study had several concerns and unmet clinical needs.

The strengths of this study design are that it is appealing to those who are accustomed to traditional designs and also lends itself to the team. This design offers the capacity to improve the broader design, with supplemental data and also gives the researcher the flexibility to publish results separately. The shortcomings of this design are that the data from the two separate methodologies might be challenging to integrate.

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2.3. *Doctor of Philosophy (PhD) study design*

The PhD takes advantage of a mixed method design (convergent parallel/triangulation design) to obtain different but complementary data to expand quantitative results with qualitative data. The intention was also to bring together the differing strengths and non-overlapping weaknesses of quantitative methods (large sample size, trends, generalisation) with those of qualitative methods (small sample, details, in-depth) to understand more fully the various factors that could affect a study's external validity (generalisability).

To approach this systematically, it was considered that there were three stages at which external validity might be threatened (Figure 2.5):

1. At the design stage, the threat to external validity could be due to selective inclusion criteria, and as a result, the potential recruits are unrepresentative of the population. There is a potential of selection bias occurring when the study sample does not represent the population that the investigator hopes to make generalisations to.
2. Recruitment into studies can often be problematic, and quite often older frailer patients with multiple medical problems are less likely to agree to participate in studies. (151-153) Non-participation of specific groups of patients can have a poor outcome on a study's generalisability.
3. Finally, proficient reporting is essential, and studies should be reported in a way that allows clinicians to judge to whom they can reasonably be applied. Substandard reporting, therefore, threatens the assessment of the external validity of a study.

Chapter 2: Methods

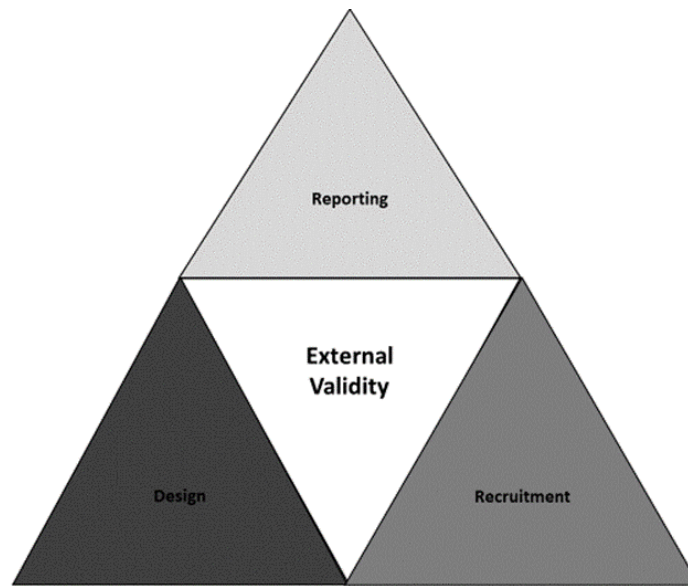


Figure 2.5: Threats to external validity at the design, recruitment and reporting stage.

The design was a predominantly quantitative mixed method study of convergent parallel/ triangulation design. (Figure 2.6) This figure also illustrates the timeline of the various arms of the study.

The quantitative arm aimed to quantify selection biases and generalisability occurring during the recruitment to EQUAL and therefore understand the applicability of observational data to the whole patient cohort. This involved a retrospective observational cohort study with patients in primary and secondary care meeting the same inclusion criteria as EQUAL.

The qualitative aspect involved semi-structured interviews with patients who agreed and who did not agree to participate in EQUAL and thus aimed to understand threats to generalisability at the recruitment stage.

The systematic review aimed to understand the threats to generalisability at the reporting stage and to determine whether the publication of the STROBE statement has improved the quality of reporting of observational studies.

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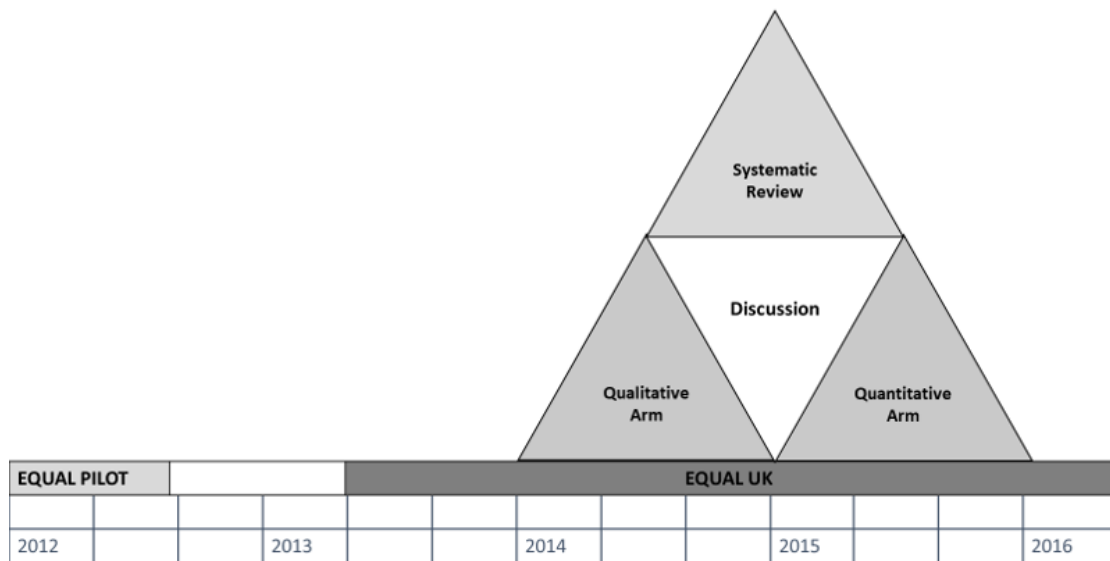


Figure 2.6: Mixed methods study design of the PhD using the convergent parallel/triangulation design

The next chapter is dedicated to the first study of this PhD, the quantitative arm which aimed to compare the patients recruited into EQUAL with patients meeting the same inclusion criteria but in primary and secondary care.

CHAPTER 3. USING PRIMARY CARE DATA TO UNDERSTAND THE GENERALISABILITY OF CLINICAL COHORTS: THE EXAMPLE OF ADVANCED CKD IN THE ELDERLY

The previous chapter set out the broad methodological approach that will be used in the Doctorate of Philosophy (PhD), a predominantly quantitative mixed methods study with three discreet studies, using the convergent parallel/ triangulation design, embedded within the multi-national European QUALity Study on the treatment of advanced chronic kidney disease (EQUAL). This chapter covers the first study of the PhD which aims to tease out the threat to generalisability as a result of selection biases that could have occurred at the design and recruitment stages of the study by using quantitative methods. It begins by summarising some of the background information presented in Chapter 1

3.1 Introduction

The Global Burden of Disease Study showed that chronic kidney disease (CKD) was one of the top 20 foremost reasons for mortality (154-157). CKD is prevalent in the elderly and is associated with increased morbidity and mortality. (158, 159) Even though patients with CKD unquestionably have enhanced the risk of advancing to end-stage renal disease (ESRD) (160), their risk of cardiovascular (CV) morbidity and mortality are more significant. (161) The EQUAL Study is an international prospective observational cohort study funded by the European Renal Association, European Dialysis and Transplant Association (ERA-EDTA)

Chapter 3: Quantitative Chapter

on treatment in advanced CKD and to determine when dialysis should be initiated in elderly patients. (129)

Cohort studies are at the top of the ladder of observational studies and are invaluable in studying rare exposures, examining multiple potential effects of a single exposure, testing multiple hypotheses and capturing adverse effects/harm in the long term. (89) The results from some well-conducted cohort studies have shown to be analogous to those from randomised trials (RCTs), though caution is still required for residual confounding unless the study is a natural experiment. (94, 162) Indeed, the international, Dialysis Outcomes and Practice Patterns Study (DOPPS), which analysed observational data using an instrumental variable approach, has influenced dialysis practice across five continents, more than any single RCT. (163) In the existing economic climate, it is also apposite that cohort studies are considerably less expensive to perform than RCTs. (86)

A general challenge of all research and particularly that of a cohort study is external validity (generalisability). (107) External validity has been discussed in detail in section 1.3 of the introduction chapter. For the results of any study to be useful, their relevance beyond the studied population needs to be understood, i.e. their generalisability. (107)

Threats to the generalisability of various clinical study designs have been well reported in the literature. (107-110) When designing a study, the researcher has to take into account the setting in which the study will be carried out, including any peculiarities of the health-care systems. This issue is particularly relevant to international studies, where the differences between health-care systems could

Chapter 3: Quantitative Chapter

potentially impact upon the outcome (results) of the study. Furthermore, differences between countries with regards to racial differences in pathology and natural history of the disease, the methods of diagnosis and disease management could also affect the generalisability of studies. (164) Selection of centres and the decision whether to recruit participants from primary, secondary and tertiary care could also have potential implications for a study's generalisability. Centre selection is likely to influence case-mix and could introduce bias in the measures of effect. For example, patients treated in tertiary hospitals (higher volume hospitals) are likely to have better clinical outcomes and in epidemiological studies can under or overestimate true prevalence of conditions (165-167). Patients managed in hospital clinics (secondary care) will differ from those managed in primary care as their disease condition is likely to be more severe and they are more likely to be symptomatic or to have other comorbidities. Alternatively, patients who are managed in the community are likely to be multi-morbid and find it difficult to attend the hospital. The above issues again will have an impact on the case-mix of a clinical study. The researcher, therefore, needs to decide, based on the research question being addressed, whether recruitment should be from all types of centre or can be restricted to one or two types with the implications that this might have for generalisability.

A significant threat to generalisability in cohort studies comes from selection bias. Cochrane collaboration defines selection bias as “systematic differences between baseline characteristics of the groups that are compared.”(168). For example, those recruited vs those not recruited, in RCTs intervention and control groups and in cohort studies exposed or unexposed subjects. In comparison with RCTs, where this is unusual and may occur as a result of the failure of randomisation or small

Chapter 3: Quantitative Chapter

sample sizes, in cohort studies selection bias occurs due to a non-random sample of a population causing some participants in the population to be less likely to be included than others(169, 170).

Miguel Delgado-Rodríguez et al. in their publication define selection bias as “The error introduced when the study population is not representative of the target population” which could occur when the participants who agree to take part in a study is not representative of the population that the researcher hopes to make generalisations to. (171) For example, patients who are frailer and sicker and do not take part in studies. (172) alternatively, linguistic or health barriers hinder participation, which results in self-selection of participants. (173) Cultural differences and socioeconomic status can also impact on willingness to participate. Such exclusions mean that the study findings cannot be generalised to the patient population that experiences the most morbidity and mortality, especially with absolute risk reduction and numbers needed to treat. (174) On the contrary, this may not be true for estimates of relative risk where the selection itself introduces a bias into the risk estimate rather than the difference between the groups for an absolute measure of risk. Because of this, conclusions about extrapolating to other populations, geographic locations or facilities need to be made with caution. One approach to deal with this is to collect information on the general population from which the study population is taken. For example, in the North American Atherosclerosis Risk in Communities (ARIC) study, generalisability was examined by nesting study patients in communities covered by broad surveillance. (97, 98) In the community surveillance component, the occurrence of myocardial infarction (MI) and coronary heart disease (CHD) death and heart failure (inpatient and outpatient) was ascertained for all residents of the

Chapter 3: Quantitative Chapter

communities. The events were investigated by review of hospital records and by query of physicians. The study showed that age-adjusted rates of MI were lower than those based on hospital discharge diagnosis code (e.g., 5.60/1000 vs 11.50/1000 among Forsyth County white men, respectively). Age-adjusted rates of definite fatal CHD were similarly lower than rates based on the underlying cause of death code (e.g., 2.82/1000 vs 4.52/1000 among Jackson black men, respectively).(175) This helped to understand the representativeness of the study participants to the broader community.

3.1.1. Aims and objectives

The aims and objectives of the first study of the PhD (main quantitative component) are as detailed below

3.1.1.1. Aim

To develop a methodology that enables us to quantify selection biases and generalisability occurring during the recruitment to observational studies and therefore to understand the applicability of observational data to the whole patient population by using existing primary care and secondary care databases.

3.1.1.2. Objectives

1. To quantify the extent of selection bias in recruitment to EQUAL and interpret the results in the context of the entire population by describing the differences in baseline demographics between patients in primary care and secondary care meeting the same inclusion criteria of those in the EQUAL Study (age ≥ 65 years and incident eGFR ≤ 20 ml/min/1.73m²).

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2. To enable the understanding of the selection that has occurred at recruitment and the generalisability of the findings to the entire population by describing differences in outcomes (patterns of hospitalization and mortality and morbidity) of CKD patients in primary care and secondary care meeting the same inclusion criteria of those in the EQUAL Study (age ≥ 65 years and incident eGFR ≤ 20 ml/min/1.73m²).

3.2 *Methods*

3.2.1 Study Design

A prospective cohort study with retrospective analysis of prospectively collected data.

3.2.2 Data Sources

3.2.2.1 The Health Improvement Network (THIN)

In the majority of general practices(GP), records are held in electronic format in Electronic Patient Records (EPRs) and are potentially available for extraction and analysis. (176) There are currently seven GP EPRs in the UK. These seven systems manage the patient data for the majority (98.9%) of patients in England, with distinct geographical variation in their distribution. (176, 177)

There are a few datasets that have been derived from primary care (GP) EPRs. Primary care patient databases reflect daily care provided to patients within a sample of practices and contain demographic information, patient-related diagnoses, and prescriptions. (176, 178,

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179) The strengths of general practice data are that they are population-based and derived from a representative subset of the population. (180, 181) The four common GP datasets have been summarised in Table 3.1.

The choice of THIN over other GP databases was mainly down to its affordability and also notably as it included access to HES linked data for the study. The other reason was due to the generalisability of the database and its validation for epidemiological studies of CKD.(180, 182-185).

The Health Improvement Network (THIN) is one of the top four electronic medical record databases and an alliance between two companies; In Practice Systems (Vision software) and IMS Health who are the guardians of the data for use in medical research. (186) The data is captured during the day to day practice and regularly sent to THIN. As of January 2014, THIN held longitudinal anonymised patient Electronic Medical Records (EMRs) from 588 of the 9,458 general practices across the UK. The database includes more than 12.4 million patients, of whom 4.7 million are currently active. The database holds information on demographics, diagnoses, prescriptions, referrals, hospitalisations, laboratory tests, immunisations, clinical measures taken within the practice, and area-level statistics such as Townsend deprivation scores. Of the 588 practices, 430 were in England, with 157 of these linked with Hospital episode statistics (HES). The data from THIN has been organised into clear, flexible

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structures as four separate files and three linked files. Table 3.2 details the various files and the information contained within them.

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Table 3.1: Summary of General Practice databases in the UK

Name	Name of Electronic Patient Record	Number of GP practices	Number of Patients	Active Patients	Coverage	Date of statistics
			(Million)	(Million)		
The Clinical Practice Research Datalink (CPRD)* (179)	Vision	674	13.7	5.0	7.1%	2/7/2013
The Health Improvement Network database (THIN)* (180)	Vision	588	12.4	4.7	6.2%	1/1/2014
Q Research (187)	Egton Medical Information Systems (EMIS)	754	13.0	NA	7%	1/5/2014
Research One (188)	System One	400	5.0	NA	NA	1/2/2013

NA=Not available, * CPRD and THIN have an overlap of some patients in both datasets.

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Table 3.2: Summary of the files within the THIN database and information contained within them.

Name of the file	Files type	Data contained in the files	Details
Patient file	Separate file	Data on demographics	Contains information on patient characteristics and registration details
Medical file	Separate file	Data on medical events	Contains details of symptoms, diagnoses and interventions recorded by the GP and the primary care team.
Therapy files	Separate file	Data on prescriptions	Contains details of prescriptions issued to patients within primary care.
Additional Health Data (AHD) file	Separate file	Data on prevention, lifestyle and diagnostics	Contains information on lifestyle data, preventative health care, immunisations, test results and death details.
Consult file	Linked file	Data on consults	Consult file provides a record of the patient consultations with information on date, time and duration.
Postcode variable indicators (PVI)	Linked file	Patients' ward/location	Contains anonymous patient postcode-linked, socioeconomic, ethnicity and environmental indices for studies using THIN Data.
Staff file	Linked file	Staff roles linked by staff ID	Contains details on the sex and roles of the practice staff that may have entered the data.

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All GPs that subscribe to the THIN database use Read codes. There are presently approximately 109,000 unique Read codes available. (189) The Read codes are a very comprehensive coded clinical language. Read Codes are a norm for reporting the care and management of patients, such as terms to cover observations (signs and symptoms), diagnosis, procedures and investigations. There are also codes for innumerable administrative purposes. The Read codes were designed and expanded by Dr James Read in 1982, for use in General Practice. The NHS acquired the Read codes from Dr Read In 1990 and made them the norm for use in the NHS. (190) The NHS has developed the codes further to cover the majority of the areas of clinical practice; which encompasses fields such as nursing, physiotherapy and health visiting.

Information on the generalisability of the results of the database to the general population is essential and assessed by comparing observed demographics, chronic condition prevalence, deprivation and deaths with UK national estimates. (34) A study looking into the generalisability of the database showed that THIN was generalisable to the UK regarding demographics and crude prevalence's of major conditions. (180, 183) but THIN and national death rates were similar only when adjusted for demographics and deprivation.

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THIN is, therefore, a reliable and useful data source for conducting research and deriving information on UK healthcare. The THIN database has also been validated for use in epidemiologic studies of chronic kidney disease. (185, 191) These studies have ascertained the prevalence of CKD 3-5 using laboratory reported eGFR and also identified a valid list of Read codes to find subjects with moderate to advanced CKD. Patient mortality data in THIN comes from information which is sent to the patient's general practitioner upon completion of the death certificate. The accuracy of diagnosis and death records in the THIN database has been previously validated with the agreement of the date of death within one day in 95% of cases and cause of death 93%. (182, 184, 192)

3.2.2.2 EQUAL (European QUALity Study on the treatment of advanced chronic kidney disease)

EQUAL is a prospective observational cohort study which recruited patients aged ≥ 65 years; with an incident eGFR of ≤ 20 ml/min/1.73m² within the last six months, regardless of subsequent eGFRs. In the UK, it recruited from March 2013 and closed recruitment in December 2015. (30) The detailed methods of the EQUAL study have been described in Chapter 2 (refer to section 2.1)

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3.2.3 Study Cohorts

3.2.3.1 The Health Improvement Network (THIN)

The following steps were taken to most closely match the THIN cohort to the EQUAL cohort.

3.2.3.1.1 Identifying patients in THIN

Suitable patients in the THIN database had to meet the EQUAL inclusion criteria with the age of ≥ 65 years and their incident (first) eGFR reading $\leq 20\text{mls/min/1.73m}^2$ after their 65th birthday. The initial extraction was carried out by IMS Health based on the following simple rules.

1. The THIN database was searched for all patients with a code for an eGFR result.
2. From patients found in step 1, the dataset was restricted to patients who were 65 and over between 01/01/2005 – 31/12/2013 (Thin was formed in 2003, but the mortality recording has been reliable since 2005).
3. From the patients identified in step 2, only those from English GP practices were included (to link to HES data).
4. From the patients found in step 3, the dataset was restricted to patients with code 1001400326 (eGFR), in the Additional Health Data (AHD) file and a data

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value ≤ 20 ml/min/1.73m² where the first reading was after their 65th birthday.

If the first reading was “0” or missing, the next reading >0 and ≤ 20 on the same day was looked up.

5. From patients found in step 4, those with a transplantation code were excluded.

3.2.3.1.2 Inclusion and Exclusion criteria (Including definitions)

To identify the primary and secondary care cohorts, the full patient history which included patient timeline and characteristics on THIN was used. Characteristics of the patients in the cohorts and reasons for exclusion were defined as follows:

a. Identifying patients with an index eGFR between 1/4/2007 to 31/12/2012

The index date was defined as the date of the first eGFR reading in the dataset ≤ 20 ml/min/1.73m². The index eGFR was the eGFR value on the index date. The cohort was restricted to patients with their first recorded drop in eGFR to ≤ 20 between 1/4/2007 to 31/12/2012 (Figure 3.1). (The Department of Health introduced universal eGFR reporting in England from 1/4/2007. (25) Hence any reported eGFR readings after this date would be based on a standardised method

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using Modification of Diet in Renal Disease (MDRD) which is based on serum creatinine that has been aligned to isotope dilution mass spectrometry (IDMS.) The 15 months before the index date was used to determine a historical baseline for each patient. The period between 1/1/2013 to 31/12/2013 was to be used to study outcomes ensuring that all patients included had a minimum of 1 year follow up. Patients with more than one eGFR reading >20 ml/min/1.73m² on the same day as the day that they had their first reading ≤ 20 mls/min/1.73m² were excluded.

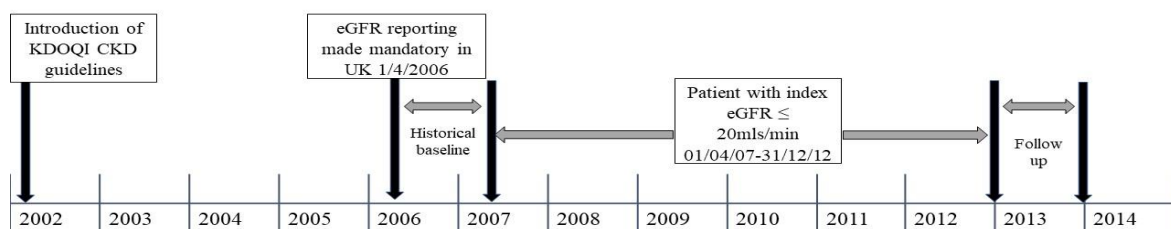


Figure 3.1: Study window for identifying the patients in primary and secondary care cohort meeting the same inclusion criteria as EQUAL

b. Identifying patients with valid patient time in THIN

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“Valid patient time” in THIN is defined as the time between the patient’s start and end dates. Start dates within THIN are defined as the latter of; Patient registration date (the date the patient registered at the GP practice), the Practice Vision date (the date that the practice started using the Vision practice management software), or the Practice Annual Mortality Rate (AMR) date (The AMR date is the year from which the GP practice is believed to be reporting all-cause mortality correspondingly in accordance with the national statistics given the practice’s demographics).

The end date within THIN is defined as the earliest of; the practice last collection date (the last collection date for actively registered patients), or the patient transfer out date (the date the patient has died or left the practice).

To have a reliable window in which the patient could have recorded $eGFR \leq 20\text{mls/min}/1.73\text{m}^2$ a study window was defined for each patient. The start of the study window was defined as the latest date out of either the start date for the practice or 1/4/2007 (1 year after the introduction of mandatory eGFR reporting). The end of the study window was the earliest date of

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either their end date or 31/12/2012 (to ensure all patients had a minimum of 1 year follow up to 31/12/2013). Any patient with an index eGFR reading outside the window was excluded.

Any patients who were not at the practice for at least three months before their index date were excluded, thereby ensuring that patients had a likelihood of having one other blood test (eGFR) before their index date. Also, patients who had transferred out of their practice within 12 months after the date that they reached eGFR of 20 ml/min/1.73m² were excluded.

c. Establishing a historical baseline

EQUAL inclusion criteria required an eGFR reading of ≤ 30 mls/min/1.73m² three months before the index event/acute event and have their first eGFR ≤ 20 mls/min/1.73m² in the last six months in patients who are attending nephrology clinic.

However, for patients in primary care (in our case, the THIN database), firstly there was a need to make the distinction between patients who have no readings before their index date and those with at least one eGFR reading. The following algorithm was used to determine the patient's historical baseline.

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- i. Any patient who had no historical readings before their index reading ($\text{eGFR} \leq 20\text{mls/min/1.73m}^2$) was excluded.
- ii. A 15-month window before the index reading was chosen to determine a historical baseline. To ensure that patients on annual review (12 monthly) had the opportunity of having a repeat blood test, a further three months added to incorporate patients who would have their blood checked late.
- iii. Any patients who only had readings beyond 15 months ago were excluded.
- iv. If patients had \geq three readings in the six months before their index date an average of their eGFR readings were taken. In patients who had <3 readings in the period six month before their index date the average for the last 15 months was taken.
- v. Patients who had an average $\text{eGFR} > 30\text{mls/min/1.73m}^2$ (in the 6 or 15 months before their index date, depending on available historical data) were excluded.

The patients identified by this approach were the closest match to those identified by the EQUAL

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inclusion criteria (without yet applying the rule in EQUAL related to attending a nephrology clinic).

d. Renal Replacement Therapy (RRT) codes before the index date

Patients with RRT related codes (dialysis and transplantation read codes) within THIN or International Classification of Disease (ICD) 10 and Classification of Interventions and Procedures (OPCS) codes within Hospital Episodes Statistics (HES) - prior to the index date were excluded (refer to Appendix 3.1 for RRT codes), thereby excluding patients with previous history of dialysis or transplantation as per the EQUAL inclusion criteria.

e. Defining the Primary and Secondary care cohort

There are two ways of identifying speciality referral in the THIN database in the medical file: 1. The variable “nhsspec”, 2. The variable “medcode (readcode)”. In the HES database, speciality referral can be derived from the variables “mainspef” & “treatspef” relating to the HES OPD speciality code for Nephrology.

The primary care cohort was defined as a random sample of eligible cases from the THIN database not attending nephrology services. Within the THIN/HES

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linked database, this was defined as patients with no speciality referral code over the full patient history either THIN GP database (**nhsspec** or **medcode** (readcode)) (Refer to the Appendix 3.2) or HES OPD code (**mainspef** & **treatspef**).

The secondary care cohort was defined as a sample of eligible cases from the THIN database attending nephrology services. Therefore, patients who have either a THIN speciality code for Nephrology (**nhsspec**), readcode indicating speciality referral (**medcode**) (Refer to the Appendix 3.2) or HES OPD code suggesting patient attendance in a hospital nephrology clinic (**mainspef** & **treatspef**) were allocated to patients attending secondary care.

3.2.3.2 EQUAL

The EQUAL cohort was restricted to the first 250 patients recruited into the study in the UK. The 250th UK EQUAL patient was recruited on the 23/09/2014 and should have completed their 12 months follow up visit on or around 22/09/2015. However, given that follow-up in EQUAL was designed such that it would coincide with the patients' routine clinic visits, a further 6-week window was added to ensure all patients had completed their 12 months follow up visit. This guaranteed that the majority of the included patients

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had the opportunity to have completed a minimum of 1 year follow up. Data was therefore extracted on 15/11/2015.

3.2.4 Study Measurements

3.2.4.1 Deprivation

Socioeconomic status was estimated using the Townsend socioeconomic deprivation score; this is calculated using economic and demographic data by the patient's postcode. (193) In the THIN database, Townsend scores and urban classification were attained for each area using 2001 census data. Each output area corresponded to roughly 150 households (Lower Super Output Area-LSOA). The scores were transformed from exact scores into quintiles: five groups of identical size, numbered 1 to 5, to specify the level of deprivation of the area with one indicating least deprived and five indicating most deprived. UK postcodes were then matched to output area Townsend deprivation quintile and urban classification. The outcome was a table of all UK postcodes with a deprivation quintile. The table contains Townsend scores for Scotland, Northern Ireland, England, and Wales. Researchers do not have access to the patient postcode, and the above matching exercise was carried out by IMS Health.

For the EQUAL cohort, the Townsend quintile scores and urban classification was mapped to the EQUAL patient's postcode using the subset of postcodes in the THIN dataset. This is an advantage of

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using IMS Health's data, and this approach ensured that the method of determining the Townsend quintile and urban classification was the same in both the THIN and EQUAL datasets.

3.2.4.2 Laboratory data

Individual patient laboratory data were determined using the relevant additional health data (ahd) codes within the ahd file of the THIN database. Refer to Appendix 3.3 for ahd codes related to the laboratory data.

In EQUAL, the index eGFR was defined as the first drop in eGFR to 20 ml/min/1.73m² within the six months before the baseline visit, regardless of subsequent eGFRs. In the THIN database, this was defined as the first drop in eGFR to ≤ 20 mls/min/1.73m² over the full patient history. Patients who participated in EQUAL had their baseline visit up to 6 months+6 weeks (222 days) after the index eGFR. Laboratory data in EQUAL was captured in the case record forms (CRFs). To keep the comparison similar to EQUAL, a window was created with the start of this window being the index date and the end of the window being the earliest of the patient's end date, 31/12/2012 or 222 days from the index date, during which the blood tests measured for patients within THIN would be in a similar window to the blood tests recorded at baseline for patients within EQUAL.

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Other laboratory data included creatinine, albumin-creatinine ratio, haemoglobin, calcium, phosphate, parathyroid hormone, albumin and blood pressure. Laboratory data that were recorded on or closest to the index date within the window were considered. Units of measurement for the laboratory data were harmonised to those that were used in the EQUAL study.

3.2.4.3 Medication

Individual patient medication history was determined using the relevant British National Formulary (BNF) codes (bnfcode) within the Therapy file of the THIN database. The BNF is a book produced by the British Medical Association and the Royal Pharmaceutical Society of Great Britain. (194) It contains vital information on the prescribing, monitoring, dispensing and administration of medicines in the UK. The therapy file and the BNF codes only cover prescription issues in primary care. All prescriptions issued by the GP are recorded in the therapy file with an associated prescription date (prscdate). BNF codes were used in preference to the drug code (drugcode) as there were two or more drug codes for a single drug that differed by dosage. To keep the comparison similar to EQUAL and in keeping with recommended NHS policy restricting prescription length to 4 weeks (28 days), any prescriptions issued before 28 days of the index date were excluded. (195, 196) An individual patients' drug count was

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calculated by summing up all the unique BNF codes in the month before the index date. Patients on antihypertensives, lipid-lowering medications and anticoagulants/antiplatelet agents were also determined by creating an indicator (Binary response: Yes/No) (refer to Appendix 3.4 for BNF codes related to the class of individual medicines). Medication history in EQUAL was captured in the CRFs. This included all the drugs that each participant was taking at the baseline visit.

3.2.4.4 Comorbidity

Individual patient co-morbidity was ascertained using the variable “category” (3=diagnosis) within the medical file of the THIN database and the respective Read codes (medcode) associated with this. The Charlson Comorbidity Index was used as it has been validated to assess comorbidity and predict survival in patients with kidney disease. (197, 198) The Charlson weights associated with each comorbidity were calculated using the Read code to Charlson weight mapping previously described and validated by Khan et al. (199). The Charlson comorbidity index (CCI) was calculated for each patient by summing the individual weights. (200) CCI was used to provide a summary of comorbidity for each patient and to adjust for comorbidity burden in the regression models. The comorbidity accrued up until the index date was used to calculate the CCI.

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Co-morbidity was captured in EQUAL CRFs mainly as a binary (Y/N) response in keeping with the CCI. The CCI for the EQUAL cohort was calculated by summing the individual weights attributed to the relevant co-morbidities.

On account of having moderate to severe CKD, all patients in the study had a minimum CCI of two. Given the skewed distribution of CCI in the study population, for adjustment in the Cox-regression models, CCI was grouped into three categories (2–3, 4-5, ≥ 6) in keeping with other peer-reviewed publications. (201, 202)

Some of the individual co-morbidity components of the CCI were grouped for adjustment in the logistic regression models to preserve the degrees of freedom. Myocardial Infarction and Congestive heart failure were grouped under Cardiac, Diabetes included Diabetes without end-organ damage and Diabetes with end-organ damage (retinopathy, neuropathy, nephropathy, or brittle diabetes), Stroke included Cerebrovascular accident with mild or no residual symptoms or TIA and Hemiplegia, Other included Dementia, Peptic ulcer disease, Mild liver disease (without portal hypertension, includes chronic hepatitis), Moderate or severe liver disease and Acquired Immunodeficiency Syndrome.

3.2.4.5 General Practitioner consultations

Patient consultations with a general practitioner are recorded within the medical file of the THIN database using a unique consultation

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ID (consltid). The consultations were limited to patients seeing a doctor within the practice using the locate variable (locate=A & locate=I). (refer to Appendix 5.5 for location codes related to consultation locations). This information was not captured in the EQUAL study.

3.2.4.6 Clinical outcomes

3.2.4.6.1 Mortality

Mortality data for patients within THIN were obtained from the patient file of the THIN database using the variable “deathdat”. to calculate the time spent in the study for patients within THIN (Primary and secondary care cohort) and to align this with patients within the EQUAL study, two dates were defined for each patient (start and end date).

Selective survival bias is defined as “when a series of survivors is selected, if the exposure is related to prognostic factors, or the exposure itself is a prognostic determinant, the sample of cases offers a distorted frequency of the exposure.”(203, 204) The following steps were taken to avoid the risk of immortal time bias (survival bias). (205) Figure 3.2 illustrates the fix used to negate the risk of immortal time bias.

- a. The start of survival time for patients in the primary care cohort was the index date.

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- b. For patients in secondary care under the care of a nephrologist at the time that they became eligible (eGFR $\leq 20\text{mls/min}/1.73\text{m}^2$), the average time spent by EQUAL patients from the index date to the 1st study visit (116 days) was added to the index date.
- c. For patients within secondary care that were referred to a nephrologist after they became eligible, six weeks was added to the referral date (the date referred to a nephrologist) in addition to the average time spent by EQUAL patients from the index date to the 1st study visit (116 days).

The end of survival follow up time (end date) was the date of death (deathdat) or 1 year after the start date, whichever came earlier.

In EQUAL, mortality data were captured as a part of the CRFs. The start of survival time in EQUAL was the date of the first study visit, and the end of survival follow up time was the date of death or the end of follow up.

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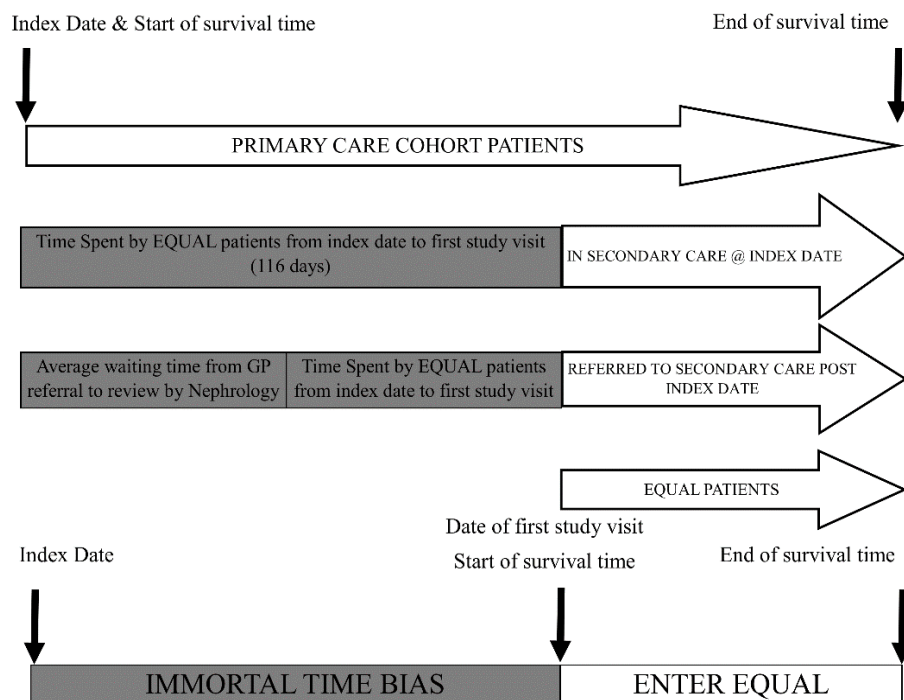


Figure 3.2: Fix introduced to negate the risk of Immortal Time Bias for each of the cohorts

3.2.4.6.2 Progression to End Stage Renal Disease (ESRD) and RRT

Progression to an $eGFR \leq 10\text{mls/min}/1.73\text{m}^2$ in the one year follow up period after reaching index $eGFR \leq 20\text{mls/min}/1.73\text{m}^2$ was calculated using the relevant ahd code for eGFR within the THIN dataset. This was taken as the point at which patients had reached ESRD. Patients that commenced RRT (dialysis or transplantation) in the 12 months after reaching index $eGFR \leq 20\text{mls/min}/1.73\text{m}^2$ were identified using read codes within THIN and ICD 10 and OPCS codes within HES (Refer to Appendix 3.1 for RRT codes). This analysis was

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not restricted to patients attending practices linked to HES. Instead, HES data were used to improve the sensitivity of detecting patients who started RRT. To harmonise with EQUAL, RRT starts were calculated for each patient between the start date and end date as in the survival calculation.

In EQUAL, RRT modality and date of the first dialysis were captured in the CRFs.

3.2.4.6.3 Hospitalisation

Within EQUAL hospitalisations between one study visit and the next were recorded retrospectively within the CRFs.

For calculating the burden of hospitalisations in the primary and secondary care cohorts, the dataset was restricted to patients attending practices linked to HES. Patient hospitalisations are registered within the HES linked file in the THIN database. The number of admissions was calculated using the count of unique admission dates (admidate). The number of days spent in hospital was calculated by subtracting the admission date (admidate) from the discharge date (disdat). To harmonise with EQUAL, hospitalisation episodes were calculated for each patient between the start date and end date.

A hospital free risk period was calculated for the patients in each of the three cohorts, firstly by calculating the risk period by

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subtracting the start date from end date for each patient, then by subtracting the number of days in hospital from the risk period and finally by adding the number of admissions to hospital to account for the risk on the day of admission. The hospital free risk period was used for adjustment in the regression model.

3.2.5 Power calculation

The power calculation considered detecting a difference in survival between the EQUAL, secondary care and primary care cohorts.

From Figure 1c in a publication by Hallan et al.,(206) the average 1-year survival rate in people with CKD aged ≥ 65 years was 82%. (206)

No data exist for secondary care and research participating patients, so based on the minimal clinically meaningful difference in survival between the two cohorts:

- primary care not referred to secondary care 82% survive one year (206)
- secondary care 87% survive one year (patients referred to secondary care)
- secondary care recruited to EQUAL 92% survive one year (patients attending the renal clinic and agreeing to participate in research)

Therefore, based on a significance level of 5% and a power of 90% the sample size required was worked out as follows:

- For the primary care and secondary care comparison (i.e. 82% vs. 87% survival), 821 in each arm.

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- For the secondary care and EQUAL comparison (i.e. 87% vs. 92% survival); 589 in each arm.

3.2.6 Statistical Analysis

Normality of the distribution of data was assessed by visual inspection of the histogram and normal probability plot. (207) Summary statistics were produced using frequencies and proportions for categorical variables, and means, standard deviations, medians and ranges for continuous variables. Categorical data were compared by χ^2 tests. Parametric continuous data were compared using a one-way analysis of variance and non-parametric using Mann-Whitney tests.

A logistic regression model was used to identify variables that were associated with being in the EQUAL cohort and to determine if the patients in EQUAL differed from a broader population of eligible patients (secondary care cohort). (208) Therefore in the model 1=Participating in EQUAL and 0=Not participating in EQUAL (Secondary care cohort) Univariable logistic regression models were built for each of the following explanatory variables: age, gender, deprivation, urban classification, individual comorbidity, CCI, haemoglobin, albumin, blood pressure and drug count. Likelihood ratio testing was used to determine whether to include variables from the univariable logistic regression model ($P < 0.2$) in the multivariable logistic regression model. Socio-demographics, laboratory variables and co-morbidity were added in a stepwise manner in the multivariable

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stepwise logistic regression analysis. The removal probability for multivariable stepwise logistic regression analysis was P values less than 0.1. A probability of $P < 0.05$ was considered to be statistically significant.

A Cox proportional hazards regression model was used to compare all-cause mortality at the one-year post-index date for patients in the primary care, secondary care and EQUAL cohort. (209) The predictor variables such as sociodemographics (index age as 5-year age bands, sex, Townsend score and rurality, laboratory variables (haemoglobin, albumin, systolic blood pressure, diastolic blood pressure) and comorbidity (CCI) were added in a stepwise manner. (199, 210, 211) Predictor variables with log-rank χ^2 P values less than 0.1 were included in the final models. The final models were checked for the assumption of proportionality using the `stphtest` command in STATA (Schoenfeld residuals) to test the proportionality of the model as a whole and also as a test of proportionality for each predictor. Predictor variables that were not proportional were included as a time-varying covariate (`tv`) in the model by using the `tv` options in the `stcox` command in Stata.

Given the over-dispersed count of hospitalisations in the three cohorts, a negative binomial regression model was used to model the count of hospitalisations with adjustment of variables as in the other regression models. (212) The models were also adjusted for hospital free period at risk.

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All analyses were performed using Stata v13.1 (College Station, TX, USA).

3.2.7 Subgroup analysis

The following subgroup analyses were carried out

1. Comparison of socio-demographic characteristics of patients in HES linked and non-HES linked practices to review for differences in the characteristics of the cohorts.
2. Comparison of socio-demographic characteristics of the incident RRT population (age ≥ 65 years) from UK Renal Registry (UKRR) compared to patients within EQUAL. One of the main aims of EQUAL was to understand the timing of dialysis start in the elderly. This subgroup analysis intended to look for systematic differences between the incident RRT patients over 65 years of age and EQUAL participants.
3. Comparison of socio-demographic characteristics of EQUAL participants with those of patients in the primary care and secondary care cohorts who were not living in the Strategic Health Authorities containing no sites taking part in EQUAL. This analysis was carried out to quantify the bias as a result of potential double counting of the EQUAL recruited patients in the secondary care cohort.

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3.3 *Results*

3.3.1 Inclusion and exclusion

Figure 3.3 shows the flow diagram for the initial extraction algorithm used by IMS health to identify suitable patients in the THIN database to meet the EQUAL inclusion criteria as stated in section 3.2.3.1. There were 15,564 patients identified by IMS Health using this algorithm from the version 1401 THIN database which was the version of the database active on the 31st of January 2014.

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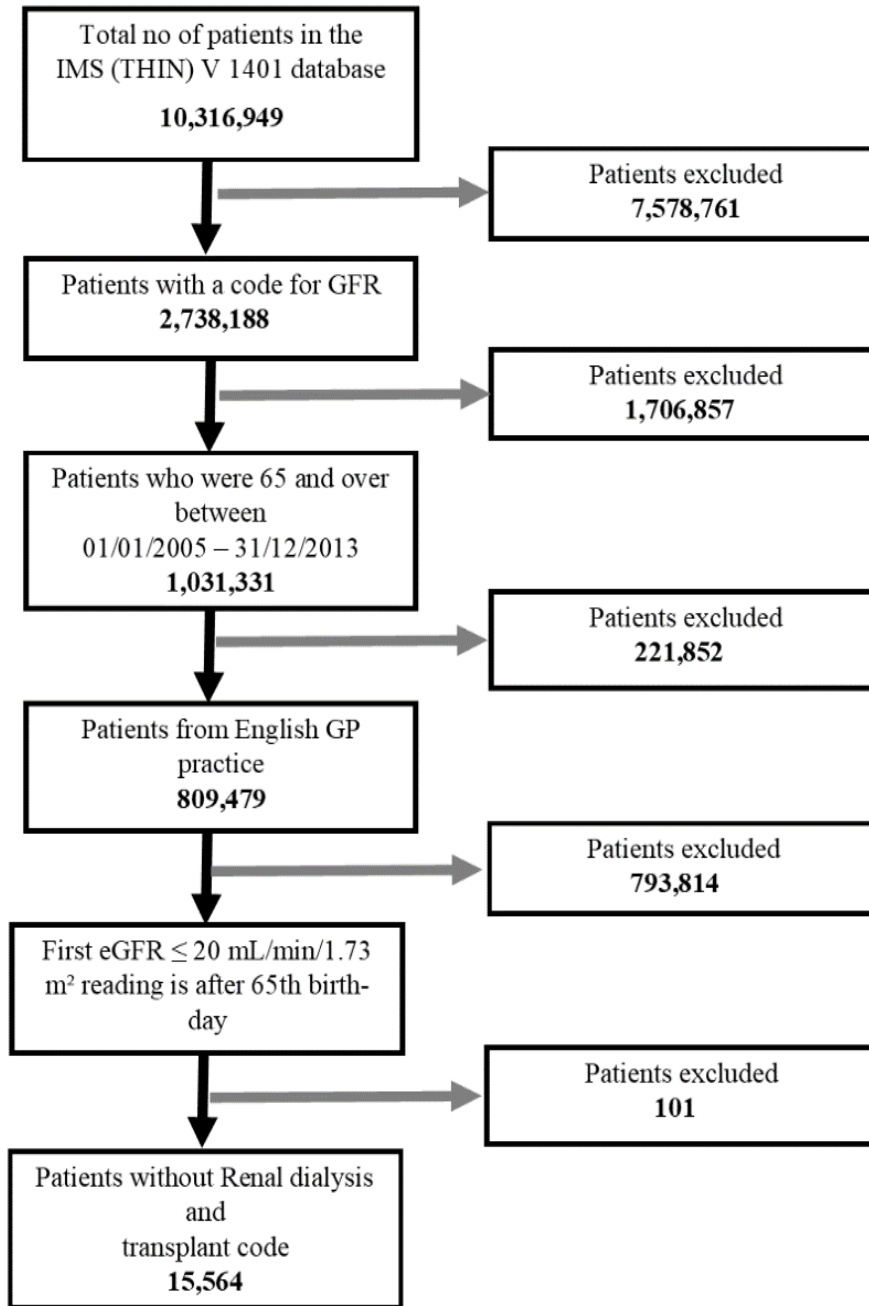


Figure 3.3: Initial extraction algorithm employed by IMS Health to identify eligible patients to meet the EQUAL inclusion criteria from the version 1401 THIN database.

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Figure 3.4 shows the flow diagram of the various exclusions that were performed on the dataset of 15,564 patients defined by IMS Health to further refine the patients to be included in the primary and secondary care cohorts that met the inclusion criteria of those recruited to the EQUAL study (Section 2.1.3.1 and 2.1.3.2 of Chapter 2).

There were 14,404 patients that had their first recorded eGFR $\leq 20 \text{ml/min/1.73m}^2$ between 1/4/2007 and 31/12/2012. Of these patients, anybody who had been with their current practice for < 3 months ($n=594$) before their index date was excluded as it would not have been feasible to calculate their historical baseline. Patients who had not contributed to follow up because of having transferred out of their practice within 12 months after their index date (508) were excluded. Patients with other eGFR readings on the index date that was $> 20 \text{ ml/min/1.73m}^2$ ($n=44$) were excluded. Patients with codes (READ, ICD10, OPCS) indicating RRT prior to index date ($n=340$), with no historical eGFR readings prior to index date ($n=1967$), no historical readings in the 15 months prior to index date ($n=3200$), and patients with baseline eGFR readings $> 30 \text{ml/min/1.73m}^2$ in the 15 months prior to index date were all excluded.

3.3.1.1 Identifying Primary care cohort

Of the 3,986 patients who met the timeline and eGFR related inclusion criteria, 889 patients from non-HES linked practices were excluded as despite

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having no speciality referral codes within THIN, they could not be reliably included in the primary care cohort without confirmation within HES. Restricting to HES linked practices ensured that the patients in the primary care cohort had not been under the care of a nephrologist at any point over their full history. There were 633 patients from practices that were linked to HES and had had no referral data to nephrology services both in the THIN database (nhsspec or readcode) or in the HES outpatient database (mainspef & treatspef), and these patients formed the primary care cohort.

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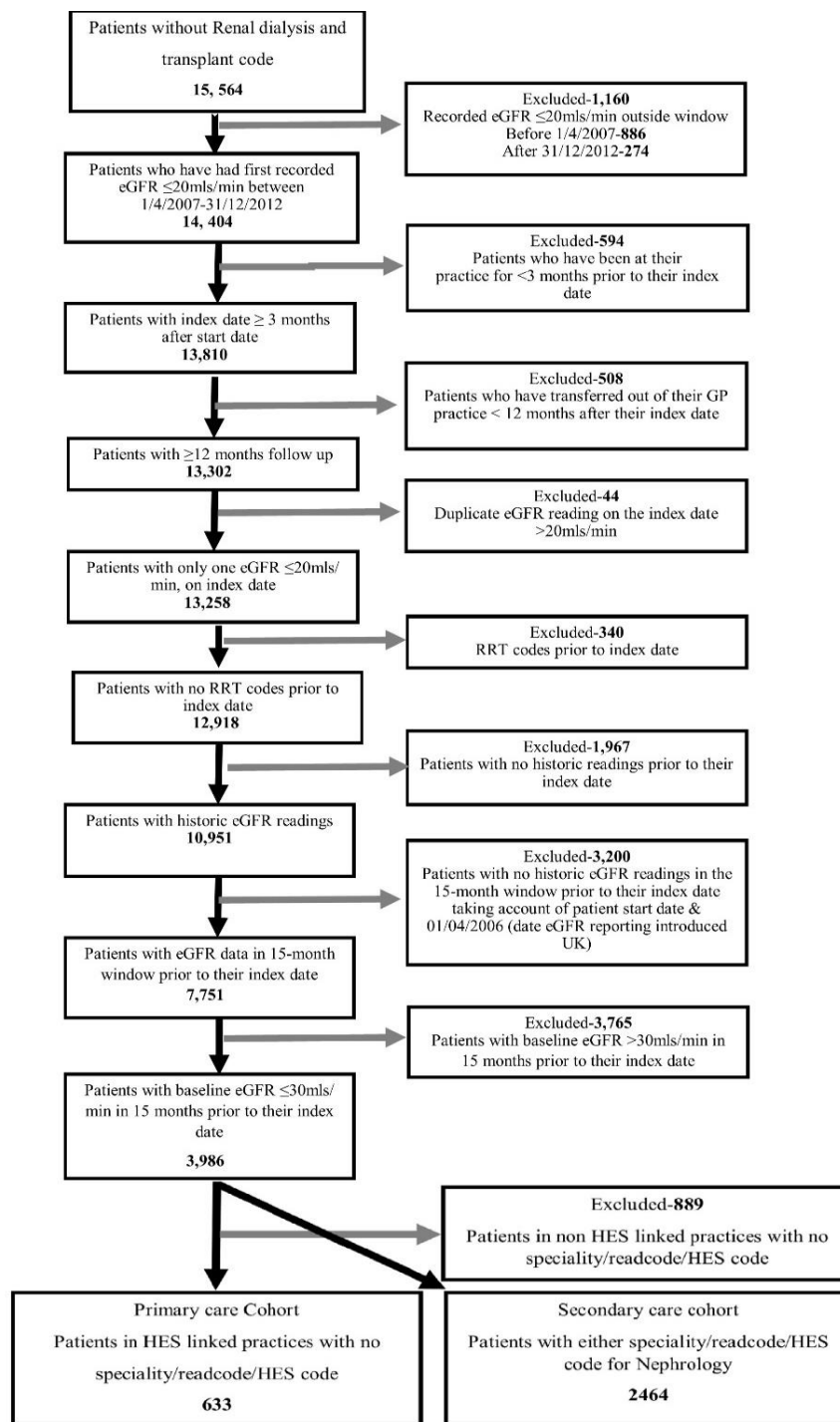


Figure 3.4: Flow diagram of the various inclusion and exclusion criteria to further refine the patients to be included in the primary and secondary care cohorts that met the EQUAL study inclusion criteria.

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3.3.1.2 Identifying the secondary care cohort

There were 2,464 patients that were identified as under the care of a nephrologist either via a THIN speciality referral code (nhsspec), a readcode within THIN (medcode), or who had a HES speciality referral code (mainspef & treatspef). Of the 2,464 patients, 1,833 were under the care of nephrologist before reaching $eGFR \leq 20\text{mls/min}/1.73\text{m}^2$ (index date) and 631 patients were referred post index date. Figure 3.5 shows a breakdown of patients coded as attending Nephrology either in THIN (nhsspec or readcode) or HES.

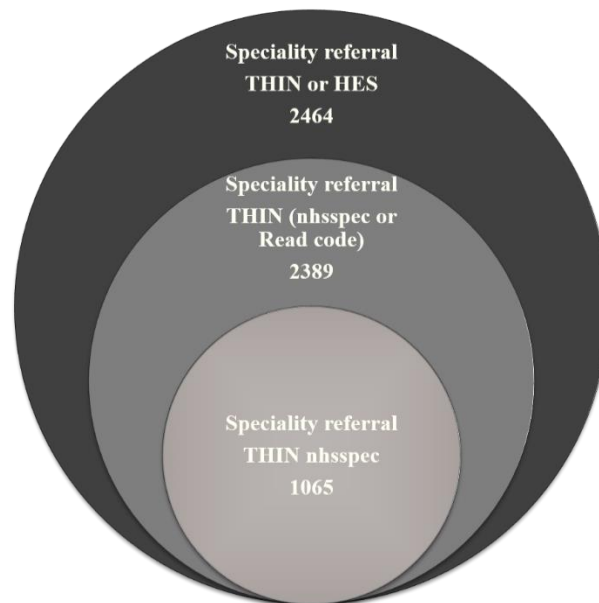


Figure 3.5: Patients with speciality referral code for nephrology in THIN (nhsspec or readcode) or HES

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3.3.2 Patient Characteristics

There were 633 patients in the primary care cohort, 2,464 patients in the secondary care cohort and 250 in the EQUAL cohort. The baseline characteristics of the patients in the three cohorts are shown in Table 3.3. Patients in the primary care, and secondary care cohorts were an average ten years and three years older, respectively when compared to patients in the EQUAL study. There was a significantly higher proportion of male participants in the EQUAL study (60.0%) when compared to patients who met the EQUAL inclusion criteria in the primary (34.8%) and secondary care cohort (51.4%) ($P < 0.001$). There were a higher proportion of patients in the EQUAL study in the most deprived Townsend quintile (28.4%) compared to those in primary and secondary care cohort (11.2% & 13.6%). EQUAL participants were more likely to be living in an urban postcode (86.4%) than patients in the Primary and Secondary care cohort (72.4% and 80.3%, respectively).

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Table 3.3: Distribution of socio-demographic characteristics in the three cohorts

Patient Characteristics		Primary care cohort N=633	Secondary care cohort N=2,464	EQUAL N=250	the χ^2 test for the difference in 3 cohorts P value
Age at index date: mean (95% CI)		86.3 (85.8-86.8)	79.7 (79.4-79.9)	76.6 (75.8-77.4)	<0.001
Index age categories N (%)	≥ 65 - <70	17 (2.7)	237 (9.6)	47 (19.0)	<0.001
	≥ 70 - <75	19 (3.0)	426 (17.3)	58 (23.5)	
	≥ 75 - <80	59 (9.3)	571 (23.2)	58 (23.5)	
	≥ 80 - <85	142 (22.5)	654 (26.5)	54 (21.9)	
	≥ 85	395 (62.5)	576 (23.4)	30 (12.6)	
Gender=Male: N (%)		220 (34.8)	1,266 (51.4)	150 (60.0)	<0.001
Townsend* quintile N (%)	1	106 (23.6)	469 (25.5)	44 (17.6)	<0.001
	2	98 (21.6)	427 (23.2)	44 (17.6)	
	3	102 (22.5)	377 (20.5)	43 (17.2)	
	4	97 (21.4)	317 (17.2)	48 (19.2)	
	5	51 (11.2)	251 (13.6)	71 (28.4)	
Urban Rural N (%)	Urban	330 (72.4)	1482 (80.3)	216 (86.4)	<0.001
	Town & Fringe	91 (20.0)	227 (12.3)	18 (7.2)	
	Village & Hamlet	35 (7.7)	136 (7.4)	16 (6.4)	

* 1=least deprived, 5=most deprived

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3.3.3 Co-morbidity

Table 3.4 shows the distribution of the Charlson Co-morbidity Index (CCI) in the three cohorts. The range of CCI in the secondary care cohort was higher when compared to the primary care and the EQUAL cohort.

Table 3.5 shows the distribution of the individual component co-morbidities of the CCI. Primary care cohort had a higher proportion of patients with heart disease (myocardial infarction (19.9%) and heart failure (32.9%)) compared to secondary care (17.0% & 22.6% respectively) and the EQUAL cohort (12.0% & 11.2% respectively). The primary care cohort had higher proportion of patients with cerebrovascular disease (17.1%) and dementia (7.3%) compared to the secondary care cohort (14.7% & 1.9% respectively) and the EQUAL cohort (9.6% & 0% respectively). The secondary care cohort had a higher proportion of patients with peripheral vascular disease (16.2% vs 10.6% for primary care vs 10% for EQUAL), chronic pulmonary disease (20.6% vs 17.1% for primary care vs 17.2% for EQUAL), rheumatic disease (9.5% vs 8.1% for primary care vs 3.2% for EQUAL), peptic ulcer disease (8.8% vs 7.1% for primary care vs 2.8% for EQUAL) and diabetes mellitus (42.7% vs 24.8% for primary care vs 28.4% for EQUAL). The EQUAL cohort had a higher proportion of patients with hemiplegia (2.0% vs 0.2% for secondary care vs 0.6% for primary care), cancer (20.4% vs 16.9% for secondary care vs 18.8% for primary care)

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and liver disease (1.6% vs 0.5% for secondary care vs 0.5% for primary care) compared to secondary care and primary cohort respectively.

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Table 3.4: Distribution of Charlson Co-Morbidity Index in the three cohorts

	Primary care cohort N=633	Secondary Care cohort N=2,464	EQUAL N=250	the χ^2 test for the difference in 3 cohorts P value
Charlson Comorbidity Index Median (IQR) range	4 (3-5) 2-10	4 (3-5) 2-11	4 (2-5) 2-10	0.0002

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Table 3.5: Individual components of the Charlson Comorbidity Index (CCI)

Individual Charlson Co-morbidity	Weight	Primary Care	Secondary Care	EQUAL	the χ^2 test for the difference in 3 cohorts P value
Myocardial Infarction N (%)	1	126 (19.9)	418 (17.0)	30 (12.0)	0.017
Congestive Heart Failure N (%)	1	208 (32.9)	556 (22.6)	28 (11.2)	< 0.001
Peripheral Vascular Disease N (%)	1	67 (10.6)	399 (16.2)	25 (10.0)	< 0.001
Cerebrovascular disease N (%)	1	108 (17.1)	362 (14.7)	24 (9.6)	0.018
Dementia N (%)	1	46 (7.3)	47 (1.9)	0 (0.0)	< 0.001
Chronic Pulmonary Disease N (%)	1	108 (17.1)	504 (20.6)	43 (17.2)	0.101
Rheumatic Disease N (%)	1	51 (8.1)	233 (9.5)	8 (3.2)	0.003
Peptic Ulcer Disease N (%)	1	45 (7.1)	216 (8.8)	7 (2.8)	0.003
Diabetes Mellitus N (%)	1	157 (24.8)	1051 (42.7)	71 (28.4)	< 0.001
Diabetes with complication N (%)	2	37 (5.9)	429 (17.4)	32 (12.8)	< 0.001
Hemiplegia N (%)	2	4 (0.6)	5 (0.2)	5 (2.0)	< 0.001
Cancer N (%)	2	119 (18.8)	419 (16.9)	51 (20.4)	0.248
Metastatic Cancer N (%)	6	5 (0.8)	12 (0.5)	5 (2.0)	0.017
Mild Liver Disease N (%)	1	3 (0.5)	12 (0.5)	4 (1.6)	0.078
Moderate Liver Disease N (%)	3	0 (0.0)	3 (0.12)	1 (0.4)	0.3
AIDS N (%)	6	0 (0.0)	1 (0.04)	0 (0)	0.836

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3.3.4 Medication

Table 3.6 shows the distribution of the medication count in the three cohorts and the proportion of patients on drugs to prevent progression of CKD such as anti-hypertensives, antiplatelet & anti-thromboembolic drugs and lipid-lowering drugs. Although the overall medication burden was similar between the three cohorts, EQUAL had a higher proportion of patients on antihypertensive (92.4% vs 76.4% for secondary care vs 73.1% for primary care), lipid-lowering drugs (69.2% vs 49.9% for secondary care vs 36.2% for primary care) and thromboembolic/antiplatelet drugs (59.6% vs 48.2% for secondary care vs 51.7% for primary care) when compared to the secondary care and primary care cohort respectively.

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Table 3.6: Distribution of the medication burden and the proportion of patients on medicines to prevent the progression of chronic kidney disease in the three cohorts in the four weeks before the index date.

	Primary care cohort N=633	Secondary care cohort N=2,464	EQUAL N=250	the χ^2 test for the difference in 3 cohorts P value
Number of Drugs Median (IQR) Range	8 (5-11) 0-22	8 (4-10) 0-31	7 (5-10) 1-19	0.43
Number on Antihypertensive N (%)	462 (73.1)	1,882 (76.4)	231 (92.4)	<0.001
Number on Lipid-lowering drugs N (%)	229 (36.2)	1,229 (49.9)	173 (69.2)	<0.001
Number On Antiplatelet/Anticoagulant N (%)	327 (51.7)	1,188 (48.2)	149 (59.6)	0.001

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3.3.5 Laboratory data

Table 3.7 shows the baseline laboratory data in the three cohorts. Although there were statistically significant differences, most of the baseline mean laboratory variables and blood pressure readings, the absolute values were clinically similar between the three cohorts. There was a clinically significant difference in Albumin Creatinine Ratio (ACR) with the patients in the EQUAL cohort having ACR two and eight times the value compared to the secondary care and primary care cohort respectively. This could potentially explain the difference between the cohorts with regards to referral to secondary care and progression to ESRD.

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Table 3.7: Baseline laboratory variables by three cohorts

Patient laboratory data	Primary care cohort N=633	Secondary care cohort N=2,464	EQUAL N=250	the χ^2 test for the difference in 3 cohorts P value
Index eGFR (ml/min/m²): [N] mean (95% CI)	[633] 17.4 (17.2-17.6)	[2,464] 17.9 (17.8-18.1)	[250] 17.4 (17.1-17.8)	<0.001
Creatinine (μmol/l): [N] mean (95% CI)	[631] 267.1 (261.5-272.7)	[2460] 270.5 (267.7-273.4)	[250] 266.6 (257.8-275.5)	<0.001
Albumin Creatinine Ratio (ACR) (mg/mmol): [N] mean (95% CI)	[116] 16.5 (-10.7-43.6)	[765] 71.2 (61.7-81.8)	[50] 136.2 (94.8-177.6)	<0.001
Haemoglobin (g/dl): [N] mean (95% CI)	[529] 11.2 (10.5-11.9)	[2149] 11.9 (11.6-12.2)	[246] 11.4 (10.4-12.4)	<0.001
Calcium (mmol/l): [N] mean (95% CI)	[261] 2.35 (2.32-2.37)	[1345] 2.32 (2.31-2.33)	[236] 2.33 (2.31-2.35)	0.14
Phosphate (mmol/l): [N] mean (95% CI)	[180] 1.37 (1.33-1.42)	[1121] 1.32 (1.31-1.34)	[237] 1.26 (1.22-1.30)	0.016
Parathyroid Hormone (PTH) (pmol/l): [N] mean (95% CI)	[11] 14.3 (-1.3-29.9)	[292] 20.8 (17.8-23.9)	[198] 19.2 (15.5-22.9)	<0.001
Albumin (g/l): [N] mean (95% CI)	[473] 37.3 (36.8-37.7)	[2076] 38.2 (38.0-38.4)	[242] 38.5 (37.8-39.2)	<0.001
Systolic BP (mmHg): [N] mean (95% CI)	[435] 129.1 (127.1-131.2)	[2209] 136.8 (135.9-137.7)	[246] 144.6 (141.8-147.4)	0.40
Diastolic BP (mmHg): [N] mean (95% CI)	[435] 70.0 (70.0-71.1)	[2209] 71.0 (70.6-71.5)	[246] 71.9 (70.5-73.3)	0.14

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3.3.6 General practitioner consultations

Table 3.8 shows the median number of general practitioner consultations in the 12 months before the index date in the primary and secondary care cohort. EQUAL was a study based on secondary care, and hence this data was not available for EQUAL patients. Patients in the secondary care cohort had a higher median number of consultations with their GP compared to the primary care cohort (9 IQR (5-15) vs. 7 (IQR 3-13), $p=0.0001$).

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Table 3.8: General Practitioner consultations in the 12 months before the index date in the Primary and Secondary care cohort

	Primary care cohort N=633	Secondary Care cohort N=2,464	EQUAL N=250	the χ^2 test for the difference in 2 cohorts P value
Number of GP consultations in 12 months prior to index eGFR Median (IQR) range	7 (3-13) 0-91	9 (5-15) 0-119	Not available	0.0001

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3.3.7 Variables associated with participation/non-participation in EQUAL

Each variable in Table 3.9 (univariable model) was considered and fitted in individual univariable models. All the models shown in Table 3.9 were restricted to patients with 100% completeness for all variables (1,436 patients in the secondary care cohort and 242 patients in EQUAL). All variables with $P < 0.2$ in the univariable models were selected for multivariable logistic regression analysis: age, sex, Townsend quintile rurality, haemoglobin, systolic blood pressure and categorised components of the CCI as described in section 3.2.6 of methods section (univariable model in Table 3.9). The multivariable logistic analysis identified five main independent factors with $P < 0.2$ associated with participation in EQUAL, namely age, gender, Townsend quintile, systolic blood pressure and co-morbidity (multivariable model 3 in Table 3.9). Increasing age was associated with non-participation in EQUAL with patients ≥ 85 years of age 75% less likely to participate. Women were 38% less likely to participate, and patients in the Townsend quintile 4 were twice and in Townsend quintile 5 four times more likely to participate when compared to the least deprived patients (Townsend quintile 1). Patients who were less likely to take part in EQUAL included those with heart disease (37% less likely), peripheral vascular disease (46% less likely), stroke (32% less likely) and

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rheumatological disease (67% less likely). Patients with a current or history of cancer were 55% more likely to participate.

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Table 3.9: Univariable and multivariable models showing variables associated with participation in EQUAL, odds ratio (OR) and (p-value)

Secondary care (1,436) * =0 EQUAL (242) * =1		Univariable model		Multivariable Model 1 (Socio-demographics)		Multivariable Model 2 (Model 1 + Laboratory variables)		Multivariable Model 3 (Model 2 + Co-morbidity)	
		OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Age (years)	≥65 - <70	1.0	-	1.0	-	1.0	-	1.0	-
	≥70 - <75	0.65 (0.43-0.97)	0.04	0.64 (0.41-0.99)	0.05	0.66 (0.42-1.04)	0.08	0.67 (0.42-1.07)	0.09
	≥75 - <80	0.48 (0.32-0.72)	<0.001	0.49 (0.32-0.77)	0.002	0.50 (0.32-0.79)	0.003	0.50 (0.32-0.79)	0.003
	≥80 - <85	0.39 (0.25-0.59)	<0.001	0.36 (0.23-0.56)	<0.001	0.37 (0.24-0.58)	<0.001	0.37 (0.23-0.59)	<0.001
	≥ 85	0.25 (0.15-0.40)	<0.001	0.25 (0.15-0.42)	<0.001	0.26 (0.16-0.43)	<0.001	0.25 (0.15-0.43)	<0.001
Gender	male (ref)	0.71 (0.54-0.92)	0.009	0.65 (0.49-0.87)	0.004	0.63 (0.47-0.84)	0.002	0.62 (0.46-0.84)	0.002
Townsend Quintile 1=least 5=Most deprived	1	1.0	-	1.0	-	1.0	-	1.0	-
	2	1.10 (0.71-1.70)	0.68	1.28 (0.80-2.03)	0.30	1.31 (0.82-2.09)	0.25	1.40 (0.87-2.24)	0.16
	3	1.21 (0.78-1.89)	0.39	1.30 (0.81-2.08)	0.28	1.37 (0.85-2.20)	0.20	1.46 (0.90-2.36)	0.13
	4	1.61 (1.05-2.49)	0.03	1.78 (1.12-2.84)	0.02	1.95 (1.22-3.10)	0.005	2.12 (1.32-3.40)	0.002
	5	3.02 (2.01-4.53)	<0.001	3.48 (2.23-5.44)	<0.001	3.69 (2.37-5.74)	<0.001	4.17 (2.65-6.57)	<0.001
Rurality	Urban	1.0	-	1.0	-	-	-	-	-
	Town/Village	0.64 (0.44-0.94)	0.02	0.78 (0.52-1.18)	0.24	-	-	-	-
Hemoglobin (g/dl)	(≥ 10 (ref), <10)	0.72 (0.51-1.03)	0.06	-	-	1.36 (0.94-1.98)	0.10	-	-
Albumin (g/l)	(≥ 35 (ref), <35)	1.04 (0.76-1.42)	0.82	-	-	-	-	-	-
Systolic BP (mm Hg)	<120	0.73 (0.47-1.41)	0.17	-	-	0.73 (0.46-1.17)	0.20	0.76 (0.47-1.23)	0.27
	≥120 - ≤140	1.0	-	-	-	1.0	-	1.0	-
	>140	1.77 (1.33-2.35)	<0.001	-	-	1.76 (1.30-2.39)	<0.001	1.69 (1.24-2.30)	0.001
Diastolic BP (mm Hg)	<70	0.97 (0.72-1.30)	0.84	-	-	-	-	-	-
	≥70 - ≤80	1.0	-	-	-	-	-	-	-
	>80	1.18 (0.82-1.70)	0.38	-	-	-	-	-	-
Charlson Comorbidity Index (CCI)	2-3	1.0	-	-	-	-	-	-	-
	4-5	0.69 (0.52-0.91)	0.009	-	-	-	-	-	-
	≥6	0.68 (0.46-1.0)	0.05	-	-	-	-	-	-
Individual CCI components	Cardiac (ref=absent)	0.53 (0.38-0.73)	<0.001	-	-	-	-	0.63 (0.44-0.90)	0.01
	PVD (ref= absent)	0.58 (0.38-0.88)	0.007	-	-	-	-	0.54 (0.34-0.86)	0.009

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	Pulmonary (ref= absent)	0.80 (0.57-1.13)	0.22	-	-	-	-	-	-
	Diabetes (ref= absent)	0.94 (0.72-1.22)	0.65	-	-	-	-	-	-
	CVA (ref= absent)	0.75 (0.51-1.13)	0.16	-	-	-	-	0.68 (0.43-1.06)	0.09
	Cancer (ref= absent)	1.41 (1.03-1.93)	0.04	-	-	-	-	1.55 (1.08-2.22)	0.02
	Rheumatology (ref= absent)	0.31 (0.15-0.65)	0.0002	-	-	-	-	0.33 (0.15-0.72)	0.005
	Other (ref= absent)	0.34 (0.18-0.66)	0.0002	-	-	-	-	0.30 (0.15-0.61)	0.001
Drug count (quintile)	Q1	-	-	-	-	-	-	-	-
	Q2	1.36 (0.95-1.96)	0.1	-	-	-	-	-	-
	Q3	0.94 (0.66-1.33)	0.72	-	-	-	-	-	-
	Q4	0.99 (0.70-1.41)	0.94	-	-	-	-	-	-

* All the models included patients with 100% completeness for all variables

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3.3.8 Mortality

Figure 3.6 and Table 3.10 show the unadjusted mortality at one year for the three cohorts. The EQUAL cohort had a higher proportion of patients alive at one year (90.7%) when compared to secondary care (85%) and primary care cohort (69.6%). All the analysis were restricted to patients with 100% completeness for all predictor variables.

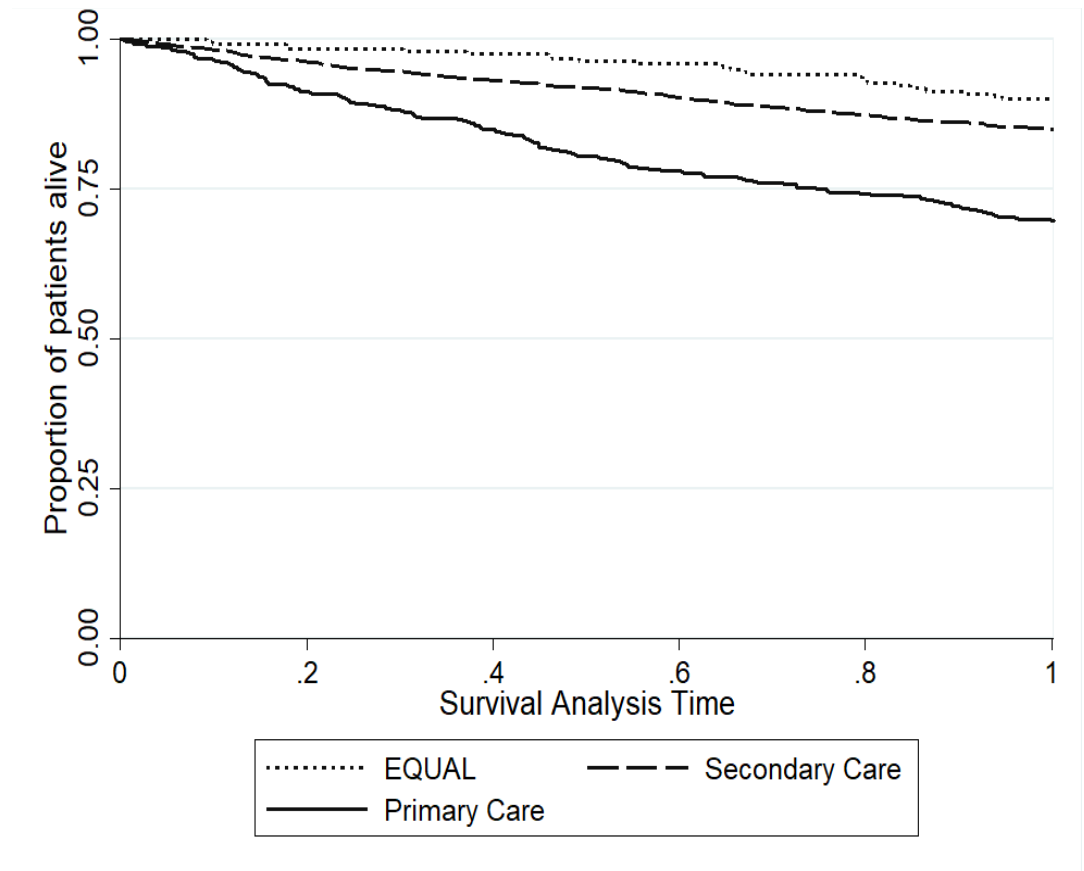


Figure 3.6: Kaplan Meier survival estimates of EQUAL, Secondary Care and Primary Care cohorts

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Table 3.10: Patient survival at one year in the EQUAL, Secondary Care and Primary Care cohort

Cohort	Patient survival at one year	
	Yes	No
	N (%)	N (%)
EQUAL	225 (90.7)	23 (9.3)
Secondary Care	1913 (85)	338 (15)
Primary Care	321 (69.6)	140 (30.4)

Table 3.11 shows the output of the final unadjusted and adjusted multivariable Cox regression models which only included predictors that were significant ($P < 0.2$) in the univariable model. Townsend quintile of deprivation was not significant in the univariable model. However, as the THIN database had a higher proportion of patients living in the most affluent areas, Townsend was retained in all the multivariable models. Only systolic blood pressure was included in the final models. Multivariable model 1 included adjustments for age, sex and Townsend deprivation quintile; model 2 included an adjustment for haemoglobin, albumin and systolic blood pressure in addition to the predictor variables included in model 1 and model 3 included adjustments for all predictors included in model 2 and CCI.

In the unadjusted model, in comparison to EQUAL, the unadjusted hazard ratio (HR) of all-cause mortality was 1.7 (95% CI 1.1-2.7, $p=0.02$) and 3.48 (95% CI 2.1-5.7, $p<0.001$) in the secondary care and primary care cohorts, respectively. In multivariable model 3, the HR reduced moderately upon adjustment for socio-demographics, laboratory variables and comorbidity. Age was the most influential

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predictor of mortality - in model 3, for every five years increase in age, there was an 18 per cent increase in the mortality ($p=0.001$). In multivariable model 3, patients with haemoglobin $<10\text{g/dl}$ had a 31% higher risk of death at one year compared to haemoglobin $\geq 10\text{g/dl}$ ($p=0.06$). Similarly, in multivariable model 3, patients with albumin $<35\text{g/l}$ had a 37% increased the risk of death compared to albumin $\geq 35\text{g/l}$ ($p=0.02$). In multivariable model 3, patients in the highest CCI category (≥ 6) had a 58% greater risk of death compared to category 2-3.

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Table 3.11: Unadjusted and adjusted 1-year all-cause mortality, hazard ratio (HR) and (p-value), for EQUAL, Secondary Care and Primary Care patients

		Unadjusted Model		Multivariable Model 1 (Socio-demographics)		Multivariable Model 2 (Model 1 + Laboratory variables)		Multivariable Model 3 (Model 2 + Comorbidity)	
Cohort		HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
EQUAL (n=236) *		1.0	-	1.0	-	1.0	-	1.0	-
Secondary Care (n=1,203) *		1.71 (1.10-2.65)	0.02	1.61 (1.03-2.52)	0.04	1.52 (0.97-2.38)	0.07	1.47 (0.94-2.31)	0.09
Primary Care (n=183) *		3.48 (2.12-5.71)	<0.001	2.80 (1.65-4.75)	<0.001	2.52 (1.47-4.32)	0.001	2.41 (1.40-4.14)	0.001
Index age (years)	5-year bands	-	-	1.19 (1.08-1.30)	<0.001	1.17 (1.07-1.28)	0.001	1.18 (1.08-1.29)	0.001
Gender	(male (ref), Female)	-	-	0.74 (0.58-0.94)	0.02	0.75 (0.59-0.96)	0.02	0.79 (0.62-1.01)	0.06
Townsend Quintile	1	-	-	1.0	-	1.0	-	1.0	-
	2	-	-	0.91 (0.64-1.29)	0.60	0.87 (0.61-1.24)	0.45	0.88 (0.62-1.25)	0.48
	3	-	-	0.97 (0.68-1.38)	0.85	0.95 (0.66-1.35)	0.76	0.95 (0.66-1.36)	0.77
	4	-	-	0.93 (0.64-1.35)	0.70	0.91 (0.63-1.33)	0.63	0.90 (0.62-1.31)	0.58
	5	-	-	1.07 (0.73-1.56)	0.74	1.07 (0.73-1.56)	0.75	1.04 (0.71-1.53)	0.83
1=least 5=Most									
Haemoglobin (g/dl)	(≥ 10 (ref), <10)	-	-	-	-	1.32 (1.00-1.75)	0.05	1.31 (0.99-1.74)	0.06
Albumin (g/l)	(≥ 35 (ref), <35)	-	-	-	-	1.38 (1.06-1.81)	0.69	1.37 (1.04-1.79)	0.02
Systolic BP (mm Hg)	10 mmHg bands	-	-	-	-	0.98 (0.90-1.07)	0.69	0.99 (0.91-1.08)	0.77
tvc (p0_bp_sys_10) **		-	-	-	-	1.06 (1.00-1.13)	0.05	1.06 (1.00-1.13)	0.05
Charlson Comorbidity Index	2-3	-	-	-	-	-	-	1.0	-
	4-5	-	-	-	-	-	-	1.16 (0.88-1.53)	0.28
	≥6	-	-	-	-	-	-	1.58 (1.13-2.19)	0.007

* All the models included patients with 100% completeness for all variables

** Systolic BP was included as a time-varying covariate as the variable was not proportional and as the effect of a systolic BP is likely to change over time

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3.3.9 Progression to ESRD and RRT

Table 3.12 shows the percentage of patients whose renal function had deteriorated to $eGFR \leq 10\text{mls/min}/1.73\text{m}^2$ in the 1-year follow up period after the start date but not had commenced RRT. Progression rates were slower for the patients in the primary care cohort with only 3% dropping to $eGFR \leq 10\text{mls/min}/1.73\text{m}^2$ when compared to 5.3% for patients in secondary care cohort ($p < 0.001$).

Table 3.12: Percentage of patients who had dropped to $eGFR \leq 10\text{mls/min}/1.73\text{m}^2$ at one year in the secondary care and primary care cohort but were not on RRT

Cohort	Percentage of patients who had fallen to $eGFR \leq 10\text{mls/min}/1.73\text{m}^2$ at one year	
	Yes	No
	N (%)	N (%)
EQUAL	NA	NA
Secondary Care	117 (5.3)	2086 (94.7)
Primary Care	14 (3.0)	447 (97.0)

NA: Not available

Table 3.13 shows the percentage of patients who commenced RRT in the 1-year follow up period after the start date. EQUAL had a higher proportion of patients starting RRT compared to those in the secondary care cohort (8.1% vs. 2.1%, $p < 0.001$). There were no patients who started RRT in the primary care cohort in this one year follow up period.

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Table 3.13: Percentage of patients on RRT at one year in the EQUAL, secondary care and primary care cohort

Cohort	Percentage of patients on RRT at one year	
	Yes	No
	N (%)	N (%)
EQUAL	20 (8.1)	228 (91.9)
Secondary Care	48 (2.1)	2203 (97.9)
Primary Care	0 (0)	461(100)

3.3.10 Hospitalisation

Table 3.14 shows the percentage of patients having zero, one, two, three or four or more hospital admissions in the 1-year follow up period after the start date. Patients in the secondary care cohort had a higher proportion of patients having three or four or more admissions (6.7% & 7.8%) compared to the primary care (2.8% & 5.0%) and the EQUAL cohort (2.8% & 1.6%).

Table 3.14: Percentage of patients having hospital admissions in primary care, secondary care and EQUAL cohorts

Number of admissions	Primary Care	Secondary Care	EQUAL
	N (%)	N (%)	N (%)
0	287 (62.3)	639 (58.3)	163 (65.7)
1	97 (21.0)	195 (17.8)	51 (20.6)
2	41 (8.9)	104 (9.5)	23 (9.3)
3	13 (2.8)	73 (6.7)	7 (2.8)
≥ 4	23 (5.0)	85 (7.8)	4 (1.6)

Table 3.15 shows the output of the final unadjusted and adjusted negative binomial regression models which only included predictors that

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were significant ($P < 0.2$) in the univariable model. All the models (Model 1 to 4), were adjusted for a patient's hospital free period at risk (as defined in section 3.2.4.6 clinical outcomes). Patients in the primary and secondary care cohort had over twice the rate of hospital admissions compared to patients in EQUAL. Increasing age was associated with 6% (IRR 0.94, 95%CI 0.86-1.02) fewer hospital admissions in the fully adjusted model (model 4). Females were 23% (IRR 0.77, 95%CI 0.61-0.78) less likely to have a hospital admission in the fully adjusted model (model 4). Albumin (< 35 g/l) was associated with risk of admission in the fully adjusted model (model 4). Charlson categories (4-5 and ≥ 6) were associated with 35%, and 50% respectively increased the risk of admission in the fully adjusted model (model 4).

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Table 3.15: Unadjusted and adjusted 1-year hospitalisation, incidence rate ratio (IRR) and (p-value), for EQUAL, Secondary Care and Primary Care patients

		Model 1* (Unadjusted Hospital free risk period)		Model 2* (Model 1+Socio-demographics)		Model 3* (Model 2 + Laboratory variables)		Model 4* (Model 3 + Comorbidity)	
Cohort		IRR (95% CI)	p value	IRR (95% CI)	p value	IRR (95% CI)	p value	IRR (95% CI)	p value
EQUAL (238) **		1.0	-	1.0	-	1.0	-	1.0	-
Secondary Care (625) **		2.13 (1.59-2.86)	<0.001	2.55 (1.90-3.44)	<0.001	2.50 (1.68-3.74)	<0.001	2.28 (1.68-3.10)	<0.001
Primary Care (229) **		1.76 (1.27-2.47)	<0.001	2.52 (1.74-3.65)	<0.001	2.58 (1.92-3.55)	<0.001	2.16 (1.44-3.23)	<0.001
Index age (years)	5 year bands	-	-	0.92 (0.85-0.99)	0.03	0.91 (0.84-0.99)	0.001	0.94 (0.86-1.02)	0.12
Gender	(male (ref), Female)	-	-	0.73 (0.60-0.89)	0.003	0.73 (0.58-0.91)	0.02	0.77 (0.61-0.98)	0.03
Townsend Quintile 1=least 5=Most	1	-	-	1.0	-	1.0	-	1.0	-
	2	-	-	1.30 (0.96-1.77)	0.09	1.29 (0.92-1.82)	0.14	1.21 (0.86-1.70)	0.27
	3	-	-	1.21 (0.88-1.66)	0.23	1.14 (0.81-1.63)	0.45	1.15 (0.81-1.63)	0.44
	4	-	-	1.28 (0.93-1.75)	0.13	1.41 (0.99-1.99)	0.06	1.38 (0.98-1.94)	0.07
	5	-	-	1.12 (0.79-1.58)	0.52	1.16 (0.80-1.69)	0.44	1.07 (0.74-1.55)	0.73
Haemoglobin (g/dl)	(≥ 10 (ref), <10)	-	-	-	-	1.18 (0.88-1.57)	0.26	1.18 (0.89-1.57)	0.24
Albumin (g/l)	(≥ 35 (ref), <35)	-	-	-	-	1.31 (1.00-1.72)	0.05	1.35 (1.03-1.76)	0.03
Charlson Comorbidity Index	2-3	-	-	-	-	-	-	1.0	-
	4-5	-	-	-	-	-	-	1.52 (1.18-1.95)	0.001
	≥6	-	-	-	-	-	-	1.55 (1.10-2.19)	0.01

* All models were adjusted for hospital free period at risk

** Patients with 100% completeness for all variables included in the model

3.3.11 Sub-group analysis

3.3.11.1 Characteristics of patients in HES linked and non-HES linked GP practices

This analysis was carried out to look for any differences in the characteristics of patients in the HES linked and non-HES linked GP practices. Characteristics of patients in the HES linked and non-HES linked GP practices are shown in Table 3.16. Patients registered at HES-linked practices were more likely to be older than those in non-HES linked practices (mean age=82.0 yrs vs. 79.5 yrs, $p < 0.001$). A similar pattern was seen when age was analysed as five-year categories. Patients in HES-linked practices were also less likely to be men (45.2% vs. 52.2%, $p < 0.001$), with some small differences in co-morbidity, GP consultations and the average number of drugs being prescribed.

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Table 3.16: Comparison of socio-demographic variables between people registered at HES-linked and non-HES linked practices.

Patient Characteristics		Patients in HES linked practices N=1,840	Patients in non-HES linked practices N=1,257	the χ^2 test for the difference in 3 cohorts P value
Age at index date: mean (95% CI)		82.0 (81.7-82.4)	79.5 (79.1-79.9)	<0.001
Index age categories N (%)	≥ 65 - <70	133 (7.2)	121 (9.6)	<0.001
	≥ 70 - <75	221 (12.0)	224 (17.3)	
	≥ 75 - <80	337 (18.3)	294 (23.2)	
	≥ 80 - <85	462 (25.1)	334 (26.5)	
	≥ 85	687 (37.3)	284 (23.4)	
Gender=male: N (%)		832 (45.2)	656 (52.2)	<0.001
Townsend quintile* N (%)	1	326 (24.4)	250 (26.0)	0.34
	2	303 (22.7)	222 (23.2)	
	3	281 (21.0)	198 (20.7)	
	4	259 (19.4)	155 (16.2)	
	5	169 (12.6)	133 (13.9)	
Urban Rural N (%)	Urban	1049 (78.0)	764 (79.8)	0.26
	Town & Fringe	185 (13.8)	133 (13.9)	
	Village & Hamlet	110 (8.2)	61 (6.4)	
Charlson Comorbidity Index Median (IQR) range		4 (3-5) 2-11	4 (3-5) 2-10	0.04
Number of GP consultations in 12		8 (4-15)	9 (5-15)	0.03

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months prior to index eGFR Median (IQR) range	0-119	0-86	
Number of Drugs Median (IQR) range	7 (4-10) 0-31	8 (5-11) 0-29	0.03

* 1=least deprived, 5=most deprived

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3.3.11.2 Comparisons of socio-demographic variables of EQUAL and incident dialysis patients submitted to the UK Renal Registry (UKRR)

Table 3.17 gives comparisons of socio-demographic variables between the patients recruited into EQUAL and incident dialysis patients submitted to the UK Renal Registry (UKRR) aged ≥ 65 years in EQUAL and non-EQUAL centres between 2013-2015. This sub-group analysis aimed to examine the differences between patients recruited into EQUAL and incident dialysis patients submitted to the UKRR in the EQUAL recruiting centres and non-EQUAL centres. Patients in EQUAL were on an average 1.3 years older when compared to incident dialysis patients both in EQUAL and non-EQUAL centres ($p < 0.001$). There were, however, no differences seen in the gender and socio-economic distribution.

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Table 3.17: Comparison of the socio-demographic variables of patients in EQUAL with incident dialysis patients submitted to the UK Renal Registry in EQUAL centres and non-EQUAL centres in England

Patient Characteristics		Group 1 EQUAL N=250	Group 2 UKRR incident dialysis patients EQUAL centres N=599	P value 1 vs. 2	Group 3 UKRR Incident dialysis patients Non-EQUAL centres N=2520	P value 1 vs. 3
Age at index date: mean (95% CI)		76.6 (75.8-77.4)	75.3 (74.8-75.8)	<0.001	75.3 (75.0-75.5)	<0.001
Index age categories N (%)	≥65 - <70	47 (19.0)	150 (25.0)	0.02	645 (25.6)	0.01
	≥70 - <75	58 (23.5)	152 (25.4)		613 (24.3)	
	≥75 - <80	58 (23.5)	156 (26.0)		649 (25.8)	
	≥80 - <85	54 (21.9)	101 (16.9)		411 (16.3)	
	≥ 85	30 (12.6)	40 (6.7)		202 (8.02)	
Gender=male: N (%)		150 (60.0)	389 (64.9)	0.17	1610 (63.89)	0.22
Townsend* quintile N (%)	1	44 (17.6)	102 (17.1)	0.89	347 (13.8)	0.41
	2	44 (17.6)	107 (18.0)		392 (15.6)	
	3	43 (17.2)	106 (17.8)		453 (18.1)	
	4	48 (19.2)	98 (16.5)		532 (21.2)	
	5	71 (28.4)	182 (30.6)		786 (31.3)	

* 1=least deprived, 5=most deprive

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3.3.11.3 Characteristics of the patients in the three cohorts having excluded patients from the secondary care cohort who were in the Strategic Health Authority (SHA) of EQUAL recruitment sites.

Table 3.18 shows the baseline characteristics of the patients in the three cohorts having excluded patients from the secondary care cohort who were in the Strategic Health Authority (SHA) of EQUAL recruitment sites. This analysis was carried out to quantify the potential dilution because of double counting of the EQUAL recruited patients in the secondary care cohort. Reassuringly, there were similar differences in the socioeconomic distribution among patients in EQUAL, primary care and secondary care cohort as shown in Table 3.3.

Considering the issue of double counting, patients in the secondary care cohort had their first recorded drop in eGFR $\leq 20\text{ml/min/1.73m}^2$ between 1/4/2007 to 31/12/2012. The first EQUAL patient was recruited in May 2013 with their qualifying index eGFR in December 2012. Therefore, the risk of double counting the EQUAL recruited patients would have been minimal and if so the results show that there has been no change in the differences observed between the cohorts.

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Table 3.18: Distribution of socio-demographic variables in the primary, secondary care cohort who were not in the Strategic Health Authority (SHA) of EQUAL recruitment sites and EQUAL

Patient Characteristics		Primary care cohort N=633	Secondary Care cohort not in SHA of EQUAL sites N=1,329	EQUAL N=250	the χ^2 test for the difference in 3 cohorts P value
Age at index date: mean (95% CI)		86.3 (85.8-86.8)	79.9 (79.5-80.2)	76.6 (75.8-77.4)	<0.001
Index age categories N (%)	≥65 - <70	17 (2.7)	115 (8.7)	47 (19.0)	<0.001
	≥70 - <75	19 (3.0)	233 (17.5)	58 (23.5)	
	≥75 - <80	59 (9.3)	312 (23.5)	58 (23.5)	
	≥80 - <85	142 (22.5)	343 (25.8)	54 (21.9)	
	≥ 85	395 (62.5)	326 (24.5)	30 (12.6)	
Gender=male: N (%)		220 (34.8)	671 (50.5)	150 (60.0)	<0.001
Townsend* quintile N (%)	1	106 (23.6)	253 (23.1)	44 (17.6)	<0.001
	2	98 (21.6)	251 (22.9)	44 (17.6)	
	3	102 (22.5)	232 (21.2)	43 (17.2)	
	4	97 (21.4)	191 (17.4)	48 (19.2)	
	5	51 (11.2)	168 (15.3)	71 (28.4)	
Urban Rural N (%)	Urban	330 (72.4)	905 (82.4)	216 (86.4)	<0.001
	Town & Fringe	91 (20.0)	120 (10.9)	18 (7.2)	
	Village & Hamlet	35 (7.7)	74 (6.7)	16 (6.4)	

* 1=least deprived, 5=most deprived

3.4 Discussion

This study examined whether patients participating in an observational cohort study of elderly people with advanced CKD (EQUAL) were similar to “real-world” patients regarding baseline characteristics, hospitalisation and survival. Patients in EQUAL were more likely to be younger, male and from an urban setting compared to the primary and secondary care cohort patients. EQUAL patients were also less likely to have cardiovascular, cerebrovascular, peripheral vascular, rheumatic diseases and dementia. EQUAL patients were more likely to start RRT and had a higher probability of being alive at one year compared to primary and secondary care patients. The overall better health of EQUAL patients likely explained the observation that they were less liable to be admitted to hospital for illnesses.

3.4.1 Age

Patients in EQUAL were three and ten years younger than patients in the secondary care cohort and primary care cohort respectively. There were decreasing odds of participation; for every 5-year age band increase, the likelihood of participation reduced significantly (patients in age band ≥ 85 years had 75% lower odds of participating $p < 0.001$).

It has been recognised that patients recruited into a study may differ from the target population and be younger and healthier than referred and registry patients. (213, 214) This is a common problem in research, with a middle-aged group of patients more likely to enrol and patients at the extremes of ages (youngest and the oldest groups) less likely to participate (215). Often the study sample disproportionately excludes the elderly (216, 217) who have a higher burden of co-

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morbidity and therefore higher expected mortality(218). Such patients may also differ from younger participants regarding treatment effects.

The implications of this are that ‘evidence-based’ research findings based on younger patients are applied to elderly patients with comorbidities, through clinical practice guidelines. (152) The reason for the underrepresentation of elderly in studies could also be because patients who are relatively healthier and more functional are less likely to agree to participate. (219, 220) Studies have also shown that older participants who participate in research studies may be less typical of their age cohort. (221)

Solutions such as liberal inclusion criteria, improved communication, reducing respondent burden, provision of travel support or data collection in the home, involving members of the target population or gatekeepers (general practitioners) in the recruiting process in the community and to coordinate logistical challenges may facilitate the participation of older people in research. (153, 222) Unfortunately, despite these measures, as the older patients increase as a proportion of the population, those who agree to participate in RCTs and observational studies may be less representative.

3.4.2 Gender

Women were less likely to be represented in EQUAL in the UK with only 40.0% of participants in EQUAL being women when compared to 48.6% and 65.2% in the secondary care and primary care cohort (OR 0.62 (0.46-0.84) $p=0.002$). A probable explanation for a lower proportion of women in the EQUAL cohort could be due to slower progression rates in women. (223) The slower progression rates mean that there will be a smaller cohort of women reaching an incident eGFR of $\leq 20\text{mls/min}/1.73\text{m}^2$ or commencing RRT as shown in Table 3.3.

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The recruitment of women in research studies is an essential issue for researchers. Medical research results cannot be extrapolated between genders as the pathophysiological process varies. For example, cardiovascular disease and some of the cancers are affected by hormones. As a result, much of our understanding of illnesses and its treatments is based on research conducted disproportionately with men. (224) However, an article by Mastroianni et al. argues that there is insufficient evidence available to determine whether women have participated in the whole of clinical studies to the same extent as men. (225, 226) It may be more complicated, however, with women no more likely than men to decline to participate in studies but merely underrepresented in target populations. (227) So if there has been no selection bias in the study, there would be fewer women in the study, but the percentage would be the same as men in the non-responder group. For example, lung cancer and cardiovascular disease are more common in men, even though they are equally severe when they affect women. More men get lung cancer than women, mainly due to patterns of smoking. With regards to cardiovascular disease, it is primarily influenced by smoking and sedentary lifestyle, and significant heart disease and stroke happen earlier in men than in women. For these reasons, it should perhaps not be surprising that we see higher numbers of men in these studies.

The variation in gender seen in EQUAL could also be explained by the variation incidence of CKD amongst men and women. Most other studies report more CKD in women and more RRT in men, however a UK based population study of the incidence of CKD by Nicholas Drey et al. showed a male preponderance which was significant in all ages (40 years or older) and increased with age. (228)

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However, this does not explain the gender differences seen between EQUAL, primary care and secondary care, using the same inclusion criteria.

3.4.3 Socioeconomic status

There was a higher proportion of patients within EQUAL in the most deprived Townsend quintile. In the multivariable logistic regression model with sociodemographic factors, Townsend quintiles 4 and 5 were two and four times more likely to participate in EQUAL, respectively. This can be explained on the basis that epidemiological studies of CKD have shown a higher prevalence of CKD with increasing deprivation. (229, 230). However, similar to gender this does not explain the socioeconomic differences seen between EQUAL, primary care and secondary care, using the same inclusion criteria. The pattern of socioeconomic status seen in the primary and secondary care cohort was the opposite of what was observed in patients recruited into EQUAL. This is in keeping with the population covered by the THIN database with a higher proportion of patients living in the most affluent areas than the national average. Therefore any analysis required adjustment for deprivation so that the estimates were closer to national death rates. (180) Socioeconomic deprivation has been associated with poorer outcomes in various chronic diseases. (231-234) Research has also shown that there is under-representation of patients in the lower socioeconomic strata in epidemiological studies, which therefore limits the generalisability of these studies.(235, 236) Negative beliefs about trials, lack of knowledge, influence of faith, healthcare provider influence (physician's lack of knowledge regarding clinical trials and poor communication skills), and

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friends' or relatives' participation in clinical trials were identified as the main barriers to participation in a systematic review. (237) However, the distribution pattern of socioeconomic deprivation in EQUAL is reassuring and in keeping with the pattern of disease prevalence rather than different rates of participation across the socioeconomic groups.

3.4.4 Rurality

An important observation was that there was a more significant proportion of patients in the secondary care cohort who lived in urban areas compared to primary care populations (80.3% vs 72.4%). This raises the possibility of referral differences between patients residing in urban and rural areas.

The recruiting sites in EQUAL were mainly academic hospitals in large cities (Birmingham, Manchester, Liverpool, Oxford, Glasgow, Bristol and Belfast), though the organisation of renal services in the UK means that they will also cover the rural areas around those cities. In the unadjusted logistic regression models, patients who lived in a town or a village were 36% less likely to participate in EQUAL (secondary care vs. EQUAL cohort). This could potentially be explained by the catchment population of the EQUAL sites. Alternatively, this observation could be due to the poor participation of patients residing in rural areas.

There is evidence to show that involvement in clinical trials can be low in patients living in rural communities.(236, 238, 239) Barriers as a result of access to healthcare may also prove to be barriers to research participation. (239, 240) Possible reasons for such hesitation include cultural beliefs, lack of knowledge, and personal attitude. To minimise

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this, patient education about research, reimbursement of the cost of travel and study visits to patients' homes may be potential solutions to be incorporated when designing a research study. (232)

3.4.5 Co-morbidity

Patients in EQUAL were less likely to have cardio-/cerebrovascular disease and rheumatological disease. In the univariate logistic regression model, higher CCI was associated with lower odds of participation in EQUAL, with patients with $CCI \geq$ four 30% less likely to participate in EQUAL (secondary care vs. EQUAL cohort). There was a higher proportion of patients in the un-referred primary care cohort with ischemic heart disease (19.9%), cerebrovascular disease (17.1%) and heart failure (32.9%) compared to patients in secondary care (17.0% 14.7% and 22.6% respectively) and EQUAL (12.0%, 9.6% and 11.2% respectively), suggesting that patients with higher co-morbidity burden are less likely to be referred to a nephrologist (secondary care). Patients with current or a history of cancer were 55% more likely to participate in EQUAL. An interesting point to consider is that as cancer (which contributes towards the CCI) appears to increase odds of participating in EQUAL (unlike all the other co-morbidities) the usefulness of using a composite index could be reduced.

The differences observed are probably not surprising as patients with ESRD have an increased risk of ischemic heart disease, cerebrovascular diseases and congestive heart failure, but fails to explain the differences between the three cohorts. Equally, all of these comorbidities are also likely to be present in patients over 80 years of age as in the primary care

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cohort. (241) Patients in the primary and secondary care cohorts had their mean age close to 80 years in comparison with a mean age of 76 years for EQUAL. In the multivariate logistic model, increasing age rather than comorbidity was significantly associated with non-participation. Also, the co-morbidity pattern seen in this study is in keeping with other published literature of elderly patients with advanced CKD, bearing in mind that all of these cohort studies may have suffered from similar selection biases to the EQUAL study. (242, 243)

3.4.6 Health outcomes

Patients in the non-referred primary care cohort and secondary care cohort had over twice the risk of hospitalisation compared to patients in EQUAL. These patients also had increased mortality at one year.

The findings of this study are consistent with prior reports in other study designs showing that patients participating in trials have better survival not only on account of being healthier but perhaps also reflecting the better medical oversight.(151, 244, 245) The hazard ratio of death in the non-referred primary care cohort compared to the referred secondary care cohort was very similar to publications by John Robert et al. (2.41 (1.40-4.14) vs 1.47 (0.94-2.31)).(36, 223, 246).

There was a higher proportion of EQUAL participants starting RRT compared to secondary care patients. The potential explanation for this finding could be that they represented a cohort of patients who had a quicker rate of progression of their kidney disease and were more likely to have had a pre-dialysis education. Due to quicker progression, this group of patients was probably under more active surveillance, which

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could have resulted in earlier detection (reaching an incident eGFR of \leq 20mls/min). The EQUAL patient invitation letters mentioned, “treatment” and “dialysis” which might have resonated more with patients who were informed about treatments for advanced chronic kidney disease such as dialysis and made them more likely to agree to participate in the EQUAL study.

Patients in the primary and secondary care cohort had over twice the rate of hospital admissions compared to patients in EQUAL. The most obvious explanation for this finding could be because EQUAL patients were younger and had a significantly lower co-morbidity burden in comparison with the patients in primary and secondary care cohort. An alternate explanation for this finding could be attributed to the source of the hospitalisation data. EQUAL hospitalisation data came from the nurse collected CRFs whereas the THIN data came from the HES linkage. It could be possible that HES linkage could have identified more hospital admissions. Also, hospital admission rates vary a lot between renal units, so it is also possible that EQUAL centres have lower rates of hospital admissions. An interesting observation was that increasing age was associated with fewer hospitalisations. A potentially be explanation could be that older patients are likely to have longer hospital admissions and therefore less likely to be admitted as often as younger patients.

3.4.7 Challenges with the use of routinely collected data

In the era of 'big data', research using routinely collected data offers more significant potential and has underpinned research in recent years. (247)

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The strengths of general practice data are that they are population-based and are derived from a representative subset of the population. (178, 180) However, the choice of GP database has to be considered prudently especially when generalising to routine care. (248) There has been relatively little research done to compare different computer systems and their advantages and disadvantages. (249, 250) Also, details about the research methods employed by researchers using primary care databases are often not described in sufficient detail to ensure replicability. (251) Payments to GPs can distort coding practice. (248) As a result of inaccurate reporting and recording of morbidity, it makes it tough to calculate a reliable denominator for calculation of incidence and prevalence. (252, 253) In summary, validation and generalisability studies of GP databases, are essential to aid researchers in choosing databases for epidemiological studies.

3.4.8 Strengths and Limitations

3.4.8.1 Strengths

This study is unique and has used routinely collected primary care data to understand the generalisability of an observational cohort study. This has therefore not necessitated the recruiting of patients who have declined to participate in a study and overcome the complex ethical issues of re-approaching patients who have already refused to take part in a study. Attempting to recruit “EQUAL declined” patients (EQUAL-D) would almost certainly still have resulted in a selected cohort. This use of routine primary care or registry data could be extended to

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understanding the generalisability of other observational and intervention studies.

3.4.8.2 Limitations

There were several limitations to this study. Identification of the appropriate comparison control group was crucial to an inference of the study as any observational design will always be limited by unmeasured confounding. (254)

The potential limitations were:

1. Although this study did not directly assess the generalisability of EQUAL data by understanding the differences in baseline socio-demographic and outcomes between EQUAL agreed and EQUAL-D, routinely collected data has shown the differences in EQUAL patients and patients in secondary care meeting the same eligibility criteria. A better comparison would have been the consent of all patients who declined EQUAL-D for their routine data to be used and for them not to participate in a study, rather than using primary care data. This approach would also be troubled with selection bias; for example, research nurses often choose not to invite patients because they are too ill at the time of invitation to participate in the study or they live far from the hospital.

In the context of this PhD, recruitment of EQUAL-D patients would have several issues:

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- i. A major ethics amendment would have been required to the EQUAL study, which was already underway. This could, however, be considered for future observational studies.
- ii. Patients would have had to sign and return a consent form. The process of consenting would have had financial implications, as the costs of mailing the consent letters and also the self-addressed envelopes.
- iii. As per the power calculation, it would have been necessary to recruit over 2000 patients into the EQUAL-D arm to have sufficient power to detect a difference in mortality between the two cohorts. One in three eligible patients who were approached agreed to participate in EQUAL. EQUAL recruited 500 patients in the UK and so even if all of the EQUAL-D patients were recruited, this would still have left a shortfall of the number needed to detect the expected difference in mortality between the groups.
- iv. It might have been ethically challenging to re-approach patients who have already refused to participate in EQUAL to consent them for their data to be used. This would be less of an issue if done at the same time as the original approach.

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- v. There would have been a further selection bias as the patients recruited into EQUAL-D would likely still have been different to the actual real-world population.
 - vi. Recruitment of EQUAL-D patients would have had an additional burden to the research nurses and could have had implications for recruitment to the primary study (EQUAL).
- 2) The other issue that was considered was applying for section 251 (Section 60 of the Health and Social Care Act 2001 as re-enacted by Section 251) approval which grants access to and use of patient identifiable information for purposes of medical research without individual patient consent. (93) At the time of drafting this PhD proposal, the Health Research Authority was currently reviewing its process for approval of section 251 support. This would have potentially resulted in delays to the PhD timelines.
- 3) The use of ineligible secondary care cohort subjects could result in bias concerning prognosis, as a result of not being able to correctly apply all the eligibility criteria as one would be able to in a prospective cohort study.
- 4) Multiple biases as a result of differences in data capture methods between THIN and EQUAL and resultant misclassification of the THIN subjects. The data in EQUAL in the setting of a study and would have been captured with

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significantly more rigour in comparison with routinely collected GP data.

- 5) This study looked at health outcomes at one year, and these short-term estimates in the EQUAL cohort may be somewhat optimistic in comparison with the primary and secondary care cohort. Some of the positive results seen in the EQUAL cohort could be explained due to the self-exclusion of patients from participation in EQUAL as a result of increased comorbidity and performance status.
- 6) THIN (primary and secondary care cohort subjects) had a higher proportion of patients living in the most affluent areas than the national average. These consistent biases could have resulted in a less fair comparison between EQUAL and THIN patients concerning survival. However, adjustment for deprivation indices in the regression models would have resulted in the accurate comparison between the cohorts and mitigated some of the biases.
- 7) The eligibility period for the EQUAL and THIN cohorts was non-overlapping. Ideally, understanding the generalisability of patients in EQUAL would require a comparison between EQUAL and the general secondary care population at the same time as the observational study is conducted. The eligibility period for THIN was between 1/4/2007 and 31/12/2012. The 250 EQUAL patients were recruited between 30/05/2013 and 22/10/2014. This issue potentially is simultaneously a

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limitation and strength of this study. Patient referral patterns from primary to secondary care would have potentially changed over the period and also the management of patients with advanced CKD would have evolved over this time.(223, 255, 256) These changes are likely to have had an impact on patient outcomes and hence upon the observations drawn from this study. Equally the fact that the eligibility period for the two cohorts was non-overlapping meant there was no double counting of patients in the secondary and EQUAL cohort and resultant dilution of effect.

3.4.9 Conclusion and recommendations

This analysis has provided empirical evidence concerning how participants in EQUAL differ from the broader population of patients that they are intended to represent. Older and sicker patients were less likely to be recruited to EQUAL, and this was supported by follow up data on health outcomes with patients in EQUAL more likely to be hospitalised and alive at twelve months. This selection pattern is likely to be found in most observational studies of chronic diseases as most chronic diseases have associated comorbidities. However, in a majority of observational studies, the classification errors, selection bias, and uncontrolled confounders and the uncertainty introduced by these types of biases are seldom quantified. Therefore, future studies would require a comparison between experimental and the eligible study population at the same time as the study is conducted as was done in the North American Atherosclerosis Risk in Communities (ARIC) study were generalisability

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was examined by nesting study patients in communities covered by broad surveillance. (97) Alternatively using statistical techniques such as probabilistic sensitivity analysis (Episens model, Orsini et al.) may help to quantify the effect of bias and researchers can report results that take into account the systematic errors and hence avoid overstating their certainty about the effect under study. (257, 258)

The next chapter seeks to understand the threats to generalisability that occur at the recruitment stage. The chapter describes a qualitative study that aimed to tease out issues underpinning patient recruitment to the EQUAL Study.

**CHAPTER 4. UNDERSTANDING PATIENTS’
PERSPECTIVES THAT COULD INFLUENCE
RECRUITMENT IN KIDNEY STUDIES: THE
EXAMPLE OF EUROPEAN QUALITY STUDY ON
TREATMENT IN ADVANCED CHRONIC KIDNEY
DISEASE-EQUAL**

The previous chapter explored threats to generalisability due to selection biases that could have occurred at the design stage of the study, and how participants in EQUAL differed from the broader population of patients that they are intended to represent. This chapter explores threats to generalisability that occurred at the recruitment stage of EQUAL by describing the methods and findings of a qualitative study that explored the thoughts and experiences of eligible patients about the recruitment process, their motivations for participation, and any perceived barriers.

4.1 Introduction

4.1.1 Recruitment to studies

The most challenging task in undertaking clinical research is participant recruitment and retention. (259) Recruitment into RCTs is often much lower than anticipated (260-262). This can be due to the study design, participants characteristics such as demographics and personal preferences, investigator features, collaboration with clinicians (115), and other barriers to patient participation, including additional demands of the study, issues with travel and costs, patient preferences and concerns about information and consent. (240) It is

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often believed that full disclosure of information, regarding both the content and the techniques and styles of delivery, could be a significant predictor of recruitment success. (263). These obstacles have been extensively studied in randomised control trials but not as robustly in observational studies. (264) In a systematic review by Lacey et al. only five of the 32 included papers discussed strategies to improve cohort follow-up, and none addressed strategies to enhance recruitment in observational cohort studies. (264) Furthermore, systematic reviews have identified many barriers but few robust interventions to improve recruitment (260, 263, 265, 266). Therefore it is not only essential to understand recruitment issues within observational studies but identifying strategies to enhance recruitment are of utmost importance.

Previous studies note that several factors may negatively influence the recruitment of older adults to clinical research, such as patient risk factors (age and comorbidity), vulnerability (frailty and cognitive difficulties) and increased clinician workload (to recruit and deal with older patients). (267-269) However, most studies have failed to seek the personal views and experiences of those in this group. Instead, many of the factors identified are based on a priori supposition or subjective observation by medical and research staff. A robust qualitative investigation is lacking. (269)

4.1.2 Older adults in clinical research

The World Health Organization (WHO) state: “The number of people aged 65 or older is projected to grow from an estimated 524 million in 2010 to nearly 1.5 billion in 2050, with most of the increase in developing countries. (270) It is therefore essential that there is equity throughout the generations when it comes to inclusion in clinical research.

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The issue of older adults participating in clinical research has been a cause for debate and growing concern for more than a decade. Some believe that age has been a cause for systematic and unethical exclusion from research and trials and an extensive amount of research suggests there is some unease about older adults being involved in clinical research.(267, 271, 272) Gonzalez et al. found that recruitment and retention of older adults were difficult, time-consuming and expensive. (273) Jacelon et al., in her paper, focuses on the challenges that researchers face when including older adults within their cohort. Jacelon suggests that the uneasiness surrounding the inclusion of older adults in clinical studies is to do with a number of apprehensions, namely: “negative stereotypes, perceived lack of competence, complications in obtaining consent, belief that they are likely to decline an invitation to participate, and the additional time needed to include them as participants”.(272) High profile and official attempts have been made to promote the inclusion of older individuals. This has been achieved through governmental and advisory documents that have set recommendations for the inclusion of older adults in research. (274-276) The established preference against the inclusion of older adults in studies and trials seems to be slowly shifting. (277) It is unsatisfactory that the results of clinical trials which consider treatments for certain conditions cannot reliably be extrapolated to older patients because the participants who take part in the studies are younger and healthier(112, 269, 278) and often do not have the complications of polypharmacy and co-morbidity that exist in older patients. (268, 279) When examining reasons for older people not being included in research, Witham & McMurdo list several key factors including study protocols, communication, attitudes and the influence of others. They then move on to list several strategies to aid the inclusion and retention of this age

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group in research. Many of the key factors found by Witham & McMurdo have been influential in the enrollment of older adults. (269) Levy et al. in his systematic review found that fifty-three per cent of health-risk behaviour clinical trials excluded adults over the age of 65, with only two and a half per cent including those only over 65 years of age. (271)

There is much more yet to be done before we can see a continuing trend of research open to involving older individuals in studies. (267, 280) Such a shift would likely prove beneficial to patient care.

4.1.3 Use of qualitative research methods to understand and optimise recruitment

Patient recruitment in clinical studies can be a challenge. Non-participation can affect not only the validity of the study but also have a financial impact. (281)

About 50% of RCTs fail to recruit to target and only 50% of those that successfully recruit do so promptly. (282) Qualitative research has been frequently used in the setting of RCTs aimed at identifying barriers to recruitment and to optimise recruitment. (283, 284) The use of Qualitative research methods has proven to be the most promising. (283) The ORRCA project (Online Resource for Recruitment research in Clinical triAls) brings together published evidence in the field of recruitment research. (285)

The qualitative research has used interviews (semi-structured; in-depth), focus groups and audio recordings not only to explore barriers to recruitment but also explore reasons for low recruitment and attempt to improve recruitment rate by implementing changes suggested by qualitative findings. (286)

A few interesting examples of the use of Qualitative research to identify barriers to recruitment are

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- i. Lack of clinician time for research (287)
- ii. conflicting roles of clinicians and Principal Investigators (288),
- iii. training needs of healthcare staff (289),
- iv. perceived barriers of clinicians to introduce RCTs (290),
- v. Doctors attitude to patient participation in trials (291)
- vi. clinicians understanding of the trial (292)
- vii. Patients strong preferences for a particular treatment (293, 294)
- viii. Communication of the RCT and clear explanation of the paucity of evidence to participants. (295, 296)

Several approaches to using qualitative research to optimise recruitment have been discussed below. (297, 298) Donovan et al. showed that the integration of qualitative research methods within a trial allows us to understand the recruitment process and elucidate changes necessary to the content and delivery of information to maximise recruitment and ensure the effective and efficient conduct of a trial. (299, 300) In the ProtecT study, the development of a complex intervention to improve recruitment was derived from the use of qualitative research and the data from interactions in on-going trial recruitment appointments. (300) The information from the interviews helped inform a set of interventions:

- i. Consistent refresher training for all staff and training for new staff in the beginning. (301)
- ii. Regular reviews of the targets for each of the centres are recorded.
- iii. Pamphlets to offer guidelines and information.
- iv. Individual feedback as needed.

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Implementation of the complex intervention in ProtecT resulted in a marked improvement in the frequency of instantaneous embracing of allocation gradually (from 65% to 81%) with the preservation of high randomisation rates (over 65%) (300).

The QuinteT Recruitment Intervention (QRI) methodology was developed by researchers at the School of Social and Community Medicine at the University of Bristol after the above set of interventions were refined in several RCTs.(302) The QRI aims to understand the recruitment process of the RCT in the recruiting centres so that reasons for recruitment problems can be recognised and suggestions made to change aspects of design, conduct, organisation or training that could then lead on to improvements in recruitment. The QRI methodology investigates the delivery of information to patients by way of audio recordings and anonymous feedback to the individuals recruiting into the RCT. A training intervention (QRI methodology) for health professionals to recruit into challenging randomised controlled trials. This intervention had a positive impact on the self-confidence of healthcare professionals in discussing RCTs with patients and also a positive impact on recruitment practice. (303) This methodology has been used in specific RCTs and has been shown to improve recruitment in some cases. (302, 304)

A potential issue to the use of embedded qualitative research in trials is the extra time, money and personnel needed to carry out the qualitative research. Therefore, the use of qualitative methods in pilot or feasibility trials before a full study would be more cost-effective by defining interventions that could be

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fully incorporated into subsequent trials. (305) Although qualitative methods have mainly been used to create interventions to improve recruitment to RCTs, these methods can be transferred to other settings such as cohort studies to have a positive effect on recruitment.

4.1.4 Qualitative Research methods

While quantitative research is widely known for generating objective, reliable and generalisable information (306), qualitative data can complement and refine this by producing rich, in-depth data on complex issues such as subjective experiences, perceptions and motivations that are difficult to quantify. (307) The use of qualitative research is invaluable in narrowing the gap in knowledge that is not easily accessible via the uses of quantitative research methodology. (308, 309)

Qualitative research lacks a single definition: Strauss and Corbin defined it by what it is not, merely stating that “by the term ‘qualitative research’ we mean any research that produces results that have not been obtained by statistical methodology or other means of quantification.”(310) Although the use of numbers in qualitative research is controversial, the distinction between quantitative and qualitative research is not entirely down to this. (311) Qualitative methods are typically inductive, in that theory and hypotheses are formulated as a result of the observations and findings. Mohr et al. described the characteristic difference between the two methods with respect to the ‘mental model’:

1. Quantitative research assumes a ‘variance theory’ approach. This methodology is associated with the analysis of the role and also the differences between the various variables.
2. The qualitative research implements a ‘process theory’ method. (312) This technique produces knowledge by studying the method by which some actions

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impact on others and provide a circumstantial and illustrative, appraisal. (307, 311)

Qualitative methods provide a way of tackling difficult topics, which are problematic or hard to measure for instance ‘how’ and ‘why’ questions. Qualitative approaches also permit wide-ranging themes to be explored, as there is less constraint placed on the information collected. This method does not impose a limitation on the variables that are collected, and these variables need not be rigidly defined. The method facilitates thorough scrutiny of the phenomena using subjective information. Henceforth, the method is invaluable for hypothesis generating or exploratory research. (307) Ormston et al. (313) have stated that qualitative research includes the following vital elements stated in Table 4.1

Table 4.1: Elements of Qualitative Research

No	Elements
1	Qualitative research provides an in-depth and interpreted understanding of the social world of participants who take part in research.
2	Qualitative research aids enhanced understanding of the participants social and material circumstances, their experiences, perspectives and histories.
3	Qualitative research uses non-standardized, flexible approaches to collecting data. This data takes account of the context (social) of the study.
4	Qualitative data is comprehensive, rich and complex.
5	Qualitative analysis retains complexity and nuance and respects the uniqueness of each participant or case as well as recurrent, cross-cutting themes.
6	Qualitative research aids openness to embryonic categories and theories at the analysis and interpretation stage.
7	Qualitative research produces outputs that include detailed descriptions of the phenomena being researched.
8	Grounded in the perspectives and accounts of participants.
9	A reflexive approach, where the role and perspective of the researcher in the research process are acknowledged. For some researchers, reflexivity also means reporting their personal experiences of ‘the field’.

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Quantitative and qualitative research methods have their distinctive merits and demerits. Instead of the methods conflicting, both the approaches should be considered in a harmonising role to each other. (314) Four possible approaches to combine qualitative and quantitative methods have been suggested by Steckler et al. (314):

1. Qualitative methods can be employed to assist the generation of quantitative measures and tools.
2. Qualitative methods can be used to get an in-depth understanding of the quantitative results.
3. Merging quantitative approaches to enhance a principally qualitative study.
4. Qualitative and quantitative research methods can be used together, equitably and in parallel.

When effected rationally, qualitative and quantitative methods together can yield fuller and wide-ranging results. Also, qualitative research methods are therefore often used by healthcare researchers to examine institutional and social practices and processes and to identify barriers and facilitators to change (315).

This thesis not only utilises the strengths of quantitative and qualitative research approaches, but the qualitative study also explores facilitators and barriers to participation in research. In this current climate, where patient-centred care and patient safety is strongly advocated (316, 317), a better understanding of patients' perceptions and experience of participation in research will undoubtedly be invaluable in guiding researchers to improve the process of inviting eligible participants to take part in research.

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4.1.5 Aims and Objectives Aim

To understand issues that underpin patient recruitment to the European QUALity Study on treatment in advanced chronic kidney disease (EQUAL study). (129)

4.1.5.2 Objectives

A qualitative interview study was nested within the EQUAL study, an observational study of advanced CKD in the elderly, and intended to recognise possible barriers to participation in research and to investigate possible resolutions to overcome the barriers.

4.2 Methods

4.2.1 Participant Eligibility

Patient interviews were conducted at three of the ten EQUAL recruitment sites, selected using recruitment data from the first few months of the study to include centres with high, medium and low recruitment rates (Bristol, Salford and Oxford respectively). Eligible participants were identified using the screening logs maintained by the local team for the EQUAL study. Eligible patients were all individuals aged 65 and over who had been approached to take part in EQUAL and had either declined or agreed.

4.2.2 Sampling Strategy

Sampling in qualitative research does not intend to detect a statistically representative set of participants. (311) Several methods of sampling exist for interview based qualitative research studies, which can overlap or be intentionally combined. Convenience sampling is probably the least rigorous approach, involving the opportunistic sampling of the readily available subjects for

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participation (318, 319). It can be associated with minimal research costs and may be appropriate for hard-to-reach groups, but can result in weak data quality which lacks credibility, and findings which lack transferability (318).

An alternative approach is purposive sampling which involves the selection of participants according to particular characteristics or experiences related to the research question of interest (318). Before sampling, the researcher will typically identify features of interest that might influence an individual's contribution to the research based on the researcher's practical knowledge of the area and sometimes knowledge of the existing literature (319). Purposive sampling also involves selection of deviant cases defined as "highly unusual cases of the phenomenon of interest or cases that are considered outliers, or those cases that, on the surface, appear to be the 'exception to the rule' that is emerging from the analysis" (320-322). Analysis of deviant cases may revise and widen the patterns emerging from data analysis.

A further approach is theoretical sampling. The iterative process of much qualitative research means that samples are often theory-driven to a greater or lesser extent (319). Theoretical sampling involves "building interpretative theories from the emerging data and selecting a new sample to examine and elaborate on this theory." (319). It involves selecting participants to test the theory, emerging themes or developing hypotheses, or to explore a specific concept further. Although theoretical sampling can be thought of as a type of purposive sampling, it must be undertaken alongside the data analysis. Theoretical sampling is the primary sampling strategy in the Grounded Theory approach (319, 323), discussed later.

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Snowball sampling, in which one participant is asked to suggest someone else who may be willing to participate, can be employed in all sampling strategies (318). In qualitative interview studies using purposive or theoretical sampling, the sample size is typically decided by attainment of theme saturation, when limited or no new concepts are emerging (324, 325), and when it is considered that no further data collection will add any new insights (323).

In this study, a purposive sampling approach was adopted for patient interviews (data collection) to achieve maximum variation regarding age (65-74 & 75 above), co-morbidity (0-2 & ≥ 3), and participation status (agreed and declined). (326-328). Care was taken so that the sample included elderly co-comorbid patients who have refused but importantly also those who have agreed to participate, the latter being 'deviant cases' for comparative analysis. Participants from the 'agreed' and 'declined' groups were interviewed with a roughly even distribution of cases in the age and co-morbid category across the three sites. The exact numbers in the groups and the sub-strata were however determined by the number required to achieve a consistent understanding across a varied group and where further interviews were not yielding any substantially new themes.

4.2.3 Recruitment

Only the local research teams had access to patient screening logs. The research teams at Oxford and Salford invited the eligible participants for qualitative interviews. In Bristol, AR was part of the research team and invited the patients for the interviews. The eligible participants were mailed the patient invitation letter and patient information sheet. The research teams in each of the centres contacted the eligible participants both in the agreed and refused group until the

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required number of participants with the defined features of interest were recruited.

Participants who were open to being interviewed had their contact details passed on to the investigator (AR). The investigator contacted the participants to arrange a suitable venue for the interview. Interviews with participants were coordinated with the outpatient clinic or follow up visits in the renal unit/hospital that usually supervises the care of the patient to reduce inconvenience to the patient. Participants were also offered the option of a home visit or telephone interview.

4.2.4 Data collection method

Interviews are a standard mode of acquiring information in a qualitative study. (329) Interviews are of three main types: structured, semi-structured and unstructured. Structured interviews allow the interviewer to ask the same questions in the same way and very much like a questionnaire with closed questioning. Therefore, a minimal range of responses is elicited. On the other end of the spectrum, unstructured interviews have very little structure and aim to discuss a limited number of topics (one or two).

For this study, it was decided that semi-structured interviews would best suit the requirements. The format of semi-structured interviews would provide the opportunity to ask open questions and to allow participants to talk privately and at length (detail) about their participation decision. This interview style would lend itself to the use of cues or prompts to encourage the interviewee to consider the question further. Other methods such as focus groups would not have been feasible as the participants were elderly and co-morbid. The logistics of coordinating such a focus group would therefore have been complicated.

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Most interviews took less than an hour to complete. Following the interview, no further participation was required.

A topic guide was used to ensure consistency and that the research aims were satisfactorily addressed, but participants were encouraged to raise the issues they considered necessary with minimal prompting, including any additional areas. This ensured that data collection was grounded in their experiences. Probing was used to clarify salient points and encourage reflection. The first draft of the topic guide was constructed to include issues drawn from a broad range of articles taken from the literature searches carried out. (330-334) Possible prompt questions were devised to access topics (Appendix 4.1 and 4.2), but in actuality, the conversation mostly moved naturally into each of the topic areas. This required a degree of skill in steering the discussion informally, replicating natural patterns of conversation. Participants could tell their own stories in their own, albeit guided, ways. This meant that the answers sought were frequently not provided in the order that questions were laid out on the form yet, through careful listening, the investigator could identify the pertinent data.

Given that the potential participants of the qualitative interviews were elderly and comorbid, it was anticipated that they would be accompanied by their spouses, other relatives or friends. It was also predicted that families and friends would answer on behalf of the participants on a few occasions but also on the rare occasion express their view on the matter. Responses from spouses, relatives or friends are denoted in quotations by an observer (O). On the occasions the family members responded to the discussion, they would be allowed to speak for the participant with efforts made to elicit the participants' views first-hand in their own words or at least to seek confirmation that the family member provided an

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accurate account. Only data (quotes) in which friends or family assist in describing the views, experiences, beliefs, perceptions of the primary participant and on the odd occasion if it was felt that friends or family's views were relevant to patients' participation decisions were included in the analysis. Any personal opinions of the friends or family are not reported in the results. To illustrate a few examples:

I: What are your thoughts on medical research?

O: I think it should be done, for the future of the children, grandchildren." OXF_DNA_16

I: When did you first come about to hear about this study called EQUAL?

R: I do not really know.

O: If we declined it though I think at the time he was probably so poorly we did not want to do it." BRL_DNA_10

Patient interviews involved a broad range of topics including factors guiding the decision to participate or not, factors about the study that appealed/did not appeal to the patient, patient ideas about research, barriers to participation at the patient healthcare interface, other obstacles to the patient involvement, patient concerns and economic incentives. Other related topics included patient satisfaction with the renal unit, patient understanding of their illness and treatment preferences. Interviews were conducted in small batches with parallel analysis, allowing insights and questions from earlier batches to inform the focus of later interviews. The topic guide evolved with each batch with emerging themes being added and redundant topics removed (Appendix 4.3 & Appendix 4.4). Interviews were audio recorded and transcribed verbatim with participants' consent, a practice recommended by Silverman. (335)

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4.2.5 Ethical Considerations

Before commencing with data collection, it was necessary to seek and gain ethical approval for the study from the NRES Committee South West - Central Bristol. This was done by submitting a substantial amendment to the EQUAL study (REC reference:13/SW/0015; Amendment number: 3, 06/12/2013; Amendment date:06 December 2013).

Individuals were given up to two weeks to consider participating. Voluntary participation was emphasised. Invited individuals were informed in the patient information sheet that they could withdraw at any time, without giving a reason. They were also informed that if they did not decide to take part, their clinical care would not be affected in any way. The participants signed a consent form at the time of the interview. Consent was obtained by myself in line with local policies and following GCP guidelines. Any clarifications required by the patients were given before the consenting process. Explicit consent for the audio recording of the interviews was requested, and participants were assured that all information would be confidential, and all data would be stored securely as per the Data Protection Act. Participants provided consent for the use of anonymised quotes in presentations and publications. Adults who were deemed unable to consent for themselves (English not first language & cognitive impairment), or to belong to vulnerable groups (mental health issues) were not approached for participation in the study.

If the patients found the interviews to be distressing, they would be allowed to pause, break, reconvene later or terminate the interview, though in practice this did not happen. Transcripts were stripped of all patient identifiers.

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4.2.6 Data Analysis Method

The general fundamentals of grounded theory underpinned the appraisal of this study and steered the data collection and analyses. (336)

Glaser and Strauss developed grounded theory in 1967. 'Pragmatism and Symbolic Interactionism' are the conceptual foundations of Grounded theory.

(337) Pragmatism deduces that 'knowledge is created through action and interaction'. Symbolic interactionism aims to 'explore behaviours and social roles to understand how people interpret and react to their environment'.(337)

Grounded theory provides a methodical means of scrutinising qualitative data and ensures the progress of a theory that is 'grounded' in the realism of the data. (336) The grounding of impressions in the data guarantees theory-observation compatibility and protects against experimenter bias (researcher performing the research influences the results). (338) Theoretical sampling, an iterative approach and constant comparisons during data analysis are the three fundamental processes of grounded theory research (Figure 4.1). (337) In grounded theory, research data collection and analysis are interconnected simultaneous processes. (338)

In this study, an iterative approach was adopted for data collection and analysis (thematic analysis). The iterative method of grounded theory consists of a series of concurrent data collection and analysis. The results from the previous cycle of data analysis advise the subsequent cycle of data collection. (339) Following this approach, interviews in this study were conducted in small batches interspersed with a preliminary analysis. Findings from early batches were used to refine the topic guide for the next set of interviews.

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Using the iterative approach enabled pertinent ideas to be recognised. As the study continued, some of these ideas were challenged, expanded, evolved, polished and explored in depth. (338) Over a period, ideas accrued in number, which became more abstract and enabled for various categories to be formed. (338) Well-defined categories offer the explanatory power to enable the development of a theory. (338)

With every cycle of sampling (interviews) generated more data which built on the previous analysis up until each of the categories got to the point of ‘saturation’. (337) Although ‘total saturation’ of data was improbable to be entirely attained, in this study ‘data saturation’ was taken as the stage in data collection when new information did not add any significant further awareness. (337)

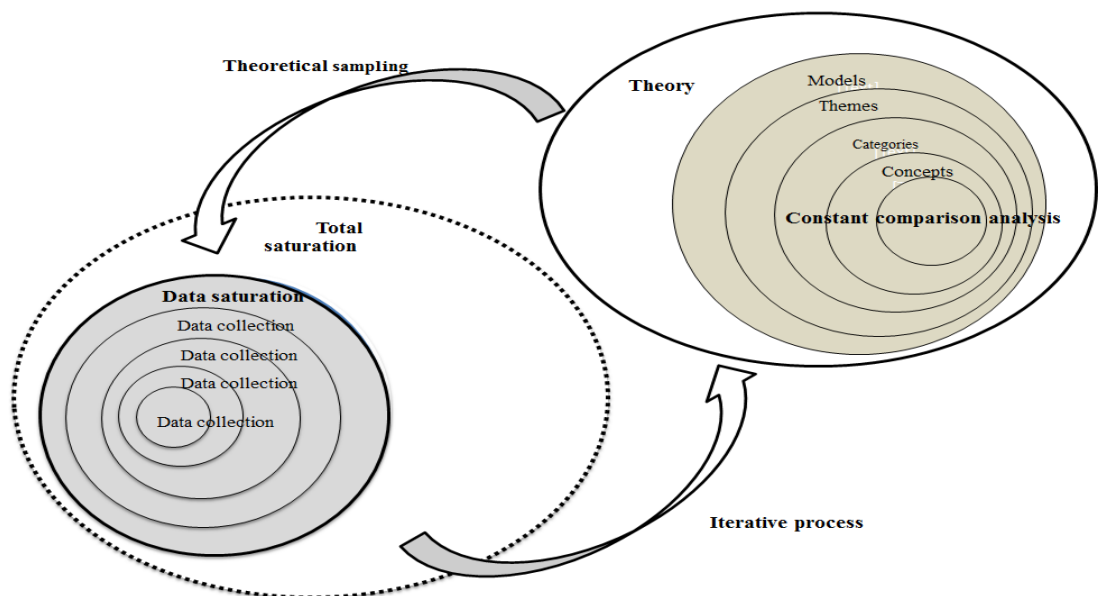


Figure 4.1: Concept of grounded theory approach (337)

In qualitative research, coding forms the foundation of data scrutiny. The code refers to “a word or short phrase that symbolically assigns a summative, salient, essence-capturing, and/or evocative attribute” for a segment of the

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data. (340) There are three types of coding which are used in grounded theory: opening coding, axial coding and selective coding. (338) The process of open coding involves a comparison of the issues of interest for parallels or variances following which codes are then allocated to the raw data. Axial coding attempts to create a relationship between the categories and codes as the codes and categories develop. In the later stages of analysis, selective coding merges all the pertinent categories around a 'core' category. (338)

In this study, thematic analysis using the constant comparison approach was selected as the most appropriate approach to organise the coded data. (341) Thematic analysis is a principle adopted from grounded theory. The long list of different codes was sorted into potential themes with some codes forming main themes or sub-themes. Thematic analysis is a commonly used method of analysis in qualitative research that can be used with any theory the researcher chooses. This allowed the participants' experiences to determine how the themes were identified from the interview data. Astin & Long comment that, in general, the intention in data analysis is not to impose an external structuring on the data but rather to use the frames or themes emerging from within the participants' comments and observations of their actions, or from other participants in other studies. (342) The research analysis, therefore, began by reading through the data (transcripts) several times and creating provisional labels for sections of data based on the meaning that emerged from the data (open coding). From this broad list of issues (labels), a categorical structure was developed consisting of several sub-topics or themes (axial coding) and identifying connections among the issues. The sub-topics were developed by listing the responses to each question (in abbreviated form) and

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then highlighting the overall subjects of each answer. Where answers were on similar themes, they were given the same sub- topic. A random subgroup of interviews was independently double coded by Dr Helen Cramer, a National Institute for Health Research (NIHR) post-doctoral research fellow in the School of Social and Community Medicine to ensure reliability. Codings were compared, and an agreed coding frame was derived that could be applied consistently to all transcripts. Any disagreements about the coding were resolved by discussion. Any new emerging themes (the raw data extracts) and its interpretation, including iteration to the coding framework was clarified with Dr Lucy Biddle, Senior Lecturer in Medical Sociology at supervision meetings. Figure 4.2 illustrates the initial coding framework extracted from NVivo. These themes were then collated under the umbrella of eight main headings (see Table 4.3, below). NVivo software (QSR International) was used to aid analysis.

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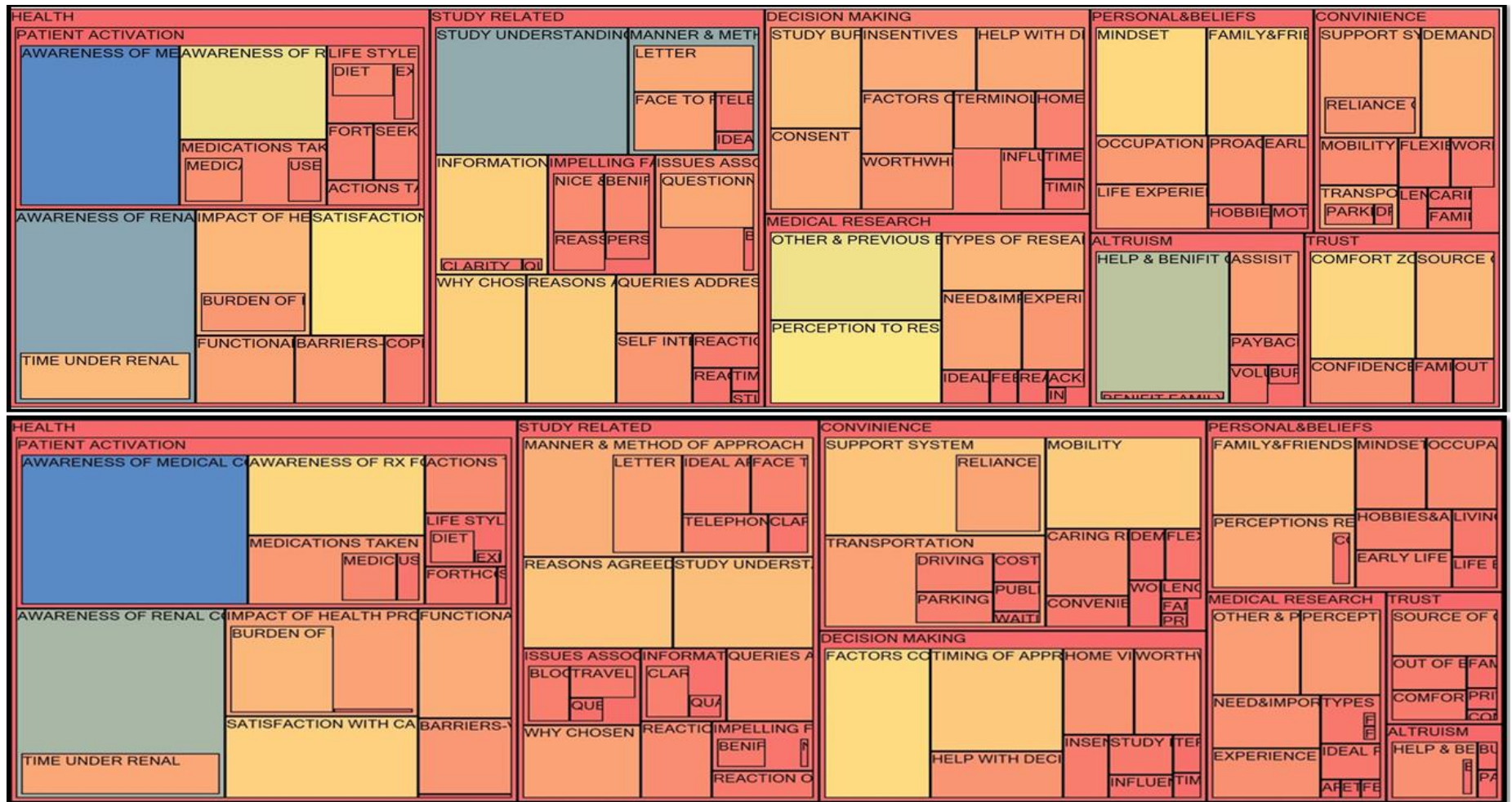


Figure 4.2: Coding framework generated from NVivo for agreed (top) and decline groups (bottom)

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The use of figures and statistics in qualitative research has been a subject of ongoing dispute. Although some qualitative researchers value the use of quantitative data to supplement the research (338, 343, 344), apprehensions about the aptness of its use persist (307, 345, 346). The use of quantitative data in qualitative research can lead to an inference of the generalisability of the conclusions with research appearing more precise, rigorous, and scientific. However, in trying to improve the rigour of qualitative research, quantitative data can lead to reducing the importance of the logic of the study and thus misrepresents the actual basis for the conclusions and ultimately has the danger of quantifying the amount of evidence. (311) It can jeopardise enforcing the ‘variance theory mental model’ on the study which theoretically weakens the strong point of the ‘process theory’ that qualitative research proposes (section 4.1.4). (311) As a result of the above discussions, this qualitative study has opted to use the verbal statements/terms such as ‘some’, ‘several’, ‘many’, ‘often’, ‘typically’, ‘sometimes’ in making any qualitative assertions. On a few instances where it was felt that there was a need to substantiate reporting of qualitative data, quantitative data was quoted to add more weight.

4.3 Results

4.3.1 Interviewer Characteristics

The interviews were carried out by the writer of this thesis, Dr Anirudh Rao (AR) (Qualifications MBBS MRCP). The investigator was a 36-year-old male, of Indian ethnicity, with a respectable command of English. He was a researcher at the UK Renal Registry (UKRR) and a doctor working in a large tertiary referral

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hospital specialising in renal medicine. AR had received formal training in Qualitative Methods, Qualitative Appraisal and the use of NVivo (347) for qualitative analysis, on taught courses at the University of Bristol. He also received guidance from Dr Lucy Biddle, Senior Lecturer in Medical Sociology, and other medical sociologists and anthropologists at the School of Social and Community Medicine, University of Bristol. In his role as a hospital doctor, the researcher was involved in the recruitment to the study in Bristol. He introduced himself to interviewees as a ‘kidney doctor who is involved in the EQUAL study’ and explained that all queries not related to the interview would be answered at the end of the interviews. Mindful of the possible effect of his expert role as a doctor (348), he stressed that he was not involved in participants medical care and had no access to their medical data. Therefore, the participant’s general practitioner (GP), supervising consultant nephrologist, or the clinical director were informed of any relevant information disclosed in the interview for continued follow-up.

4.3.2 Interview context

The semi-structured interviews were conducted between May 2014 and July 2015 about six to eight months after EQUAL recruitment had commenced in each of the three sites (Bristol, Salford and Oxford). Participants for the interviews in the agreed group had been in the EQUAL study for at least six to eight months. Participants of the agreed group had either just been followed up or had up to 6 months elapsed since their last follow up. The participants in the declined group were interviewed after 4-8 weeks following their invitation to participate in EQUAL. The timing of the interview could have influenced the participant (agreed and declined) understanding or recollection of EQUAL.

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4.3.3 Interview Setting

Face-to-face semi-structured interviews were conducted at the participants' homes between May 2014 to July 2015. Although it was envisaged that the interviews would be in the renal unit or hospital, coordinated with the outpatient clinic or follow up visits, in reality, most patients preferred home visits given the length of the interviews. Also, the difficulty of room availability in the hospital for the duration of the interview meant that home visits became the default option. Some participants had either their spouse, children, or other family members present at the interviews (6/17 agreed group, 7/17 declined group). On the occasions, the family members responded to the discussion this was handled as stated in the section 4.2.4 of the methods section.

4.3.4 Participant Characteristics

In the agreed group in EQUAL, all the participants that were invited to take part in the qualitative interviews decided to participate. Recruitment was more difficult in the declined group with only 1 in 4 participants agreeing to participate in the interviews. Despite this, every attempt was made to represent both genders and comorbidities in this declined group. Table 4.2 shows the number of interview participants by EQUAL participation status in the three sites.

Table 4.2: Distribution of patients in EQUAL sites by participation status

Participant characteristics	EQUAL participation status	
	Agreed to participate	Declined to participate
	N=17	N=17
Bristol (high recruitment site)	5	8
Salford (medium recruitment site)	6	3
Oxford (low recruitment site)	6	6

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Table 4.3 gives a breakdown of the interview participants' age and co-morbidity by EQUAL participation status. There were a higher proportion of participants aged ≥ 75 in both the agreed and declined group. In the declined group there was a more significant proportion of women compared to men. This correlates with the EQUAL recruitment data which showed that 60% of those declining to participate were women. The distribution of comorbidity was evenly distributed in both the agreed and declined groups.

Table 4.3: Participant characteristics

Participant characteristics		EQUAL participation status	
		Agreed to participate N=17	Declined to participate N=17
Age (years)	65-74	7	5
	≥ 75	10	12
Gender	Male	10	7
	Female	7	10
Comorbidity (Charlson's count)	0-2	7	7
	≥ 3	10	10

4.3.5 Interview Themes

Eight major themes emerged from interviews describing factors influencing participation and non-participation in research, the majority containing some sub-themes (Table 4.4). They are discussed below alongside illustrative data extracts. There were no significant differences in the themes by site (high, medium and low recruiting sites) and the initial recruitment rates were more likely related to the resources at these sites and competing studies.

Table 4.4: Themes describing factors influencing participation & non-participation in the EQUAL study

Major theme	Subtheme
Healthcare related issues and patient activation	Satisfaction with care
	Forthcoming with non-related symptoms

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	Awareness of renal condition and its treatment
	Awareness of medical condition
	Actions taken when unwell
	Impact of health problems
	Burden of hospital appointments
	Barriers: Vision, Hearing and memory
Altruism and Self-interest	Altruistic morals
	Self-interest/Personal Gain
Convenience	Caring responsibility
	Mobility
	Reliance on friends and family
	Home visits
	Transportation
Help with decision	-
Medical Research	Perception of research
	Previous experience
	Worthwhile
Personal and beliefs	Early life
	Family and friend's health experiences
	Proactive
	Mindset
	Privacy
Study-related	Why chosen
	Study understanding
	Reaction to invitation
	Manner and method of approach
	Timing of approach
	Clarity of invitation/information
Trust	Source of contact
	Confidence in approaching person
	Privacy

4.3.5.1 Healthcare related issues and patient activation

As mentioned in section 4.1.2, there is a vast amount of literature which argues that participants who take part in studies are younger and healthier and less likely to have the complications of polypharmacy and co-morbidity that exist in older patients. This theme captures the impact of the burden of health, and its relation to participation in EQUAL. This theme is mainly descriptive and reveals differences between the two groups about awareness of healthcare related issues, which could

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have a bearing on the participation decisions. The evidence emerging from the theme also suggests that patients who engaged in their healthcare and thus were more activated were more likely to agree to participate in research. Patients' perceptions of health and healthcare can have an impact on the choice to participate in research.

A patients' understanding of their health condition or lack of it can have a significant influence on participation in research. A couple of participants made a direct link between their awareness of their health condition and their decision whether or not to participate in EQUAL, as illustrated in the two quotes below.

"I: So, you got the letter and what happened did somebody gets in touch with you?"

R: No, only me, only me made up my mind, I thought well I ain't going to bother with that. Thinking, I have got no idea of the kidney trouble or what it is all about." BRL_DNA_15

"I: What did you think when you received the letter?"

R: Yeah, there was no definite other reason why I didn't join it, you know, I just it wasn't worth it from your point of view, you know....as far as I knew, there wasn't anything wrong with me you know, there's nothing physically wrong, let's put it that way. Moreover, that seemed to me to be; that is what I felt, that I was wasting your time." OXF_DNA_05

Further quotes related to this theme and its sub-theme are illustrated in Table 4.5 below.

4.3.5.1.1 Satisfaction with care

The sub-theme 'Satisfaction with care' captured the relationship between EQUAL participation and the interviewees' overall satisfaction with their healthcare. This theme was explored in fourteen of the seventeen participants in the agreed group, all of whom were satisfied with the care that they had received at the renal unit and overall from the NHS. In the declined group only six of the sixteen participants were happy with their care. Despite this, they had other overriding

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circumstances that had caused them to refuse participation. Seven in the declined group had neutral responses, and three were dissatisfied with the care that they had received.

Three of the participants in the agreed group felt that their experience of the renal unit influenced their decision to participate.

“R: The renal unit, I see. I have found up there; it is a different situation than the cardiology where I go, it is um, very friendly. You know, it’s quite um, like when what’s the doctors name, they all call him Dr X. You know, and everyone, different one I’ve seen, we’ve um, what can I say, we’ve just, I’ve told them different silly stories and then, and it’s been very relaxed. Moreover, of course, I think what helps, although they have moved, the smallness of the place is far more intimate so to speak. However, I have found the staff so very different than they are in cardiology. They are very helpful and very, they seem to care more about you, you know? Yes, and a good atmosphere, my partner always says that good atmosphere in, here isn’t it? I said “Yeah”.” BRL_AGREE_12

4.3.5.1.2 Forthcoming with non-related symptoms

The data coded under the subtheme of ‘Forthcoming with non-related symptoms’ explored participants’ ability to volunteer concerns about their health during consultations when not directly questioned about these. The majority of the participants in the agreed group (7/8) would bring up any non-related health concerns they might have at a consultation with their GP/Renal physician. The group that did not agree to participate seemed less likely (4/7) to bring up other health concerns not directly relating to the consultation.

4.3.5.1.3 Awareness of renal condition and its treatment

The sub-theme ‘Awareness of renal condition and its treatment’ captures interviewees’ awareness of their renal condition (CKD) and the potential treatments for this. Although the connection between this awareness of renal condition and participation was not explicitly explored in the interviews, the two

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groups were different about this theme with the majority of the participants in the agreed group being aware of the cause of their kidney failure in comparison to those in the declined group. The theme indicates that patients who agree to participate are more aware of their illness and hence this generates self-interest which drives them to participate. BRL_AGREE_10 was a negative case, contrary to the majority, who agreed despite little awareness of their renal condition. It was their altruistic moral of “help and benefit to others” (section 4.3.5.2) that had motivated them to participate in EQUAL.

I: Do you want to tell me about your kidney problems?

R: Well I do not know what you mean by that cos as far as I know they do not bother me.

I: OK. So, you have no symptoms what so ever of with your kidneys?

R: Well no not as far as I know.” BRL_AGREE_10

Nine of the 17 participants in the agreed group and only 4 of the 14 participants in the declined group were aware of the potential of requiring dialysis should their kidney disease progress. All patients recruited into EQUAL had to have an eGFR less than 20 ml/min/1.73m². Across the UK this is when the patients are likely to have received a dialysis-related education and therefore to be aware of its potential need. The majority of patients commence dialysis when they reach a mean eGFR of 8 ml/min/1.73m².

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Table 4.5: Sub-themes coded under ‘Healthcare related issues and Patient activation’ with illustrative quotes in the agreed and declined groups

Sub-theme	Agreed group (Illustrative quotes)	Declined group (Illustrative quotes)
Satisfaction with care	<p><i>I: What has your experience been so far?</i> <i>R: Renal Unit, is thoroughly relaxed, sometimes non-medical if you like, everyone’s friendly, even the nurses taking the blood.....it is a nice atmosphere in the, in the unit itself, it is not too medicalised if you like.</i> <i>I: Did your experience at the Unit have a bearing on your decision to participate in this study?</i> <i>R: I suppose in a way because it was relaxed and the whole Unit seems to be run on a nice relaxed, friendly basis rather than purely medical. It is informal, and it puts you at ease.” BRL_AGREE_11</i></p>	<p><i>I: So, this whole experience for the last year or so how ... and how would you summarise your thoughts?</i> <i>R: Rubbish. I do not consider that anybody is taking me seriously about what I can do and what I cannot do.” OXF_DNA_06</i></p>
Forthcoming with non-related symptoms	<p><i>I: If there is something else bothering you about your health do you bring it up yourself without being asked?</i> <i>R: Oh usually. I am not one of these that soldier on keeping it to myself. I have had too many things go wrong I mean I had a problem the other week with my bladder, discomfort and I thought “Right I am going to get it checked out, I have had cancer twice, I want to get it sorted” SAL_AGREE_08</i></p>	<p><i>I: If you are seeing the doctor, like your kidney doctor, or your GP, if something is in the back of your mind, or if something is bothering you, although it is not related to why you are seeing them, do you bring it up at these meetings?</i> <i>R: Not particularly, no.” OXF_DNA_01</i></p>
Awareness of renal condition and its treatment	<p><i>I: So, what have you been told is wrong with your kidney?</i> <i>R: It is got... I even know what it is called. I’ve got a staghorn stone in the right kidney, and the kidney is shrunk round it.” SAL_AGREE_06</i></p> <p><i>I: Okay, for example, should your kidneys fail, do you know what can be done?</i> <i>R: I know I asked her about the dialysis, and that is when she explained to me....” BRL_AGREE_01</i></p>	<p><i>I: So when you did get this letter through the post from Nurse M, asking you to take part in this big kidney study, what was your initial thoughts?</i> <i>R: My initial thought was; I don’t know that I’ve got anything wrong with my kidneys. I mean there is nothing obvious, I wasn’t being treated for anything, and I suggested to her that I’d probably be a waste of money or a waste of time, you know, if it went on for four years was it, or something?” OXF_DNA_05</i></p>
Awareness of medical condition	<p><i>I: And do you know what each of your medications is for and what it does?</i> <i>R: It will be easier when I show you. I can never understand the medical names. These two basically cover the blood pressure. The consultant at renal put me on this one instead of the statins; he said it was a better one for it.” OXF_AGREE_02</i></p>	<p><i>I: And do you know what each of your medications is for and what it does?</i> <i>R: I presume; I forget what they all are for now (laughter) get so many. I got a load of bloody tablets.” BRL_DNA_10</i></p>
Actions taken when unwell	<p><i>I: If you were feeling breathless, for a couple of days, okay, how would you take that forward?</i> <i>R: Wait and watch. If it got too bad, I would consult Dr X and say look, this is not, I do not seem very well. I do realise with this that I am getting short of breath, but I thought, after I went onto dialysis,</i></p>	<p><i>I: On a given day you are not feeling well, what steps do you take?</i> <i>R: I just want to sit down and go to sleep.</i> <i>O: Mum is ... she will suffer in silence. ... while I’m proactive and try and say, “Look, you need to see the doctor – we need to get you to the doctor.” She will say, “Oh, I have not felt well the last week – I feel a</i></p>

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	<i>the breathing would get better, but it does not seem to have got that much better. I saw Dr X last week, I went to the clinic last week, and I said that and he said things take a bit of time, but that is about it really.” OXF_AGREE_03</i>	<i>bit dizzy,” so I get her to the doctor and try and sort it out.” BRL_DNA_04</i>
Impact of health problems	<i>“I: OK. How do your medical problems affect you? “R: You just learn to live with things, don’t you? I do most of the things myself – cooking, and sometimes I have not washed the pots properly, and I’m not too sure... There is no sensation in my fingers to check them... I think it is just ageing, arthritis.” SAL_AGREE_07</i>	<i>“R: I come over tired all the time, and I cannot do what I want to do. Because I used to do all this gardening, even now, clean all the windows at my age – a very independent woman, and I cannot do it... Otherwise, I have been fit all my life, and I have gone downhill.” BRL_DNA_04</i>
The burden of hospital appointments		<i>“R: Well what it was, with all the clinics. I mean this is sort of like injections, foot clinic, diabetic clinic, renal clinic and the eye clinic, everybody seems to want blood..... I cannot remember, I was panicking (laughter) it is all sort of more visits and more blood.....It was “help, please, no more” was my reaction.” OXF_DNA_17</i>
Barriers: Vision, Hearing and memory	<i>“R: Well I think I’ve had one like that [Patient Information Sheet] but I don’t think I read it all it’s such a lot to read, and my eyesight isn’t quite so good as it used to be, and um it takes me a long time to read anything nowadays...I’ve got trouble with my eyes because I go to the eye hospital and um I’ve had laser treatment on one eye and twice on the other eye.” BRL_AGREE_10</i>	<i>“R: And so hearing the phone is not good, you know, sometimes it is a low frequency, low signal strength and I have difficulty understanding it. Um, and that is another reason why I, am frightened of going in for interviews and things in case I mishear or do not hear at all.” BRL_DNA_13 “I: How were you contacted, so you just received a letter did you to say? R: I had a letter. However, I have not got around to reading it because reading is difficult. R: So somebody rang me up, and I said that I had not read it.” OXF_DNA_17</i>

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BRL_AGREE_12 again was a negative case who had agreed to participate to benefit others. She expressed that the questions in the EQUAL questionnaire were not relevant to her. This suggested that the participant's assessment of their condition did not coincide with the relevance of the questions in the EQUAL study questionnaire.

“R: Well I did say to Nurse when she came after the first and left me with this thing to go through and I said to her, course a lot of this the answers or the questions here, really don't apply to me because this is, questions for people who are really suffering because of kidney problems failure and then they were talking about how would you feel about dialysis and things like that, so well I said to Nurse “the thing is I'm not that advanced” so you understand a lot of the questions were for people who were on their way into dialysis really, so I said to her “there are, there are quite a few questions here that don't apply to me at all”. BRL_AGREE_12

4.3.5.1.4 Awareness of other medical conditions

This theme describes interviewees' awareness of their co-existing medical conditions and the medications are taken for these. As described above (Table 4.2), the agreed and the declined group were balanced in the comorbidity burden. However, the interviewees in the EQUAL agreed group were more aware of their health conditions and medications compared to the declined group.

4.3.5.1.5 Actions are taken when unwell

This sub-theme describes patients engagement with healthcare and the management of their health. A majority of interviewees in the agreed group said that they would consult their GP or engage with their nephrologist if they continued to feel unwell beyond a few days in comparison to the declined group.

4.3.5.1.6 Impact of Health problems

This theme describes differences between the groups with regards to the potential impact of their health problems. Most of the patients both in the agreed and declined group had a significant impact on their ability to function because of their morbidity.

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However, despite the level of morbidity, participants in the agreed group were more mobile (see section 4.3.5.3.2), while the declined group were affected much more significantly. Participants in the agreed group appeared to be more functional overall, and those with reduced functional status were less likely to participate.

A few of the participants in the agreed group were still pursuing their hobbies, reflecting their physically active state.

*“R: I have retired, and like I said my main hobby is golf twice a week. Apart from that it is just like anyone else would do; television and computer. Nothing out of the ordinary, nothing exceptional.”
SAL_AGREE_05*

4.3.5.1.7 The burden of hospital appointments

Participants, particularly those in the declined group, had a significant number of hospital appointments because of their co-morbidities. In the agreed group 9/17 and the declined group 13/17 participants were affected by the burden of hospital appointments.

4.3.5.1.8 Barriers: Vision, Hearing and memory

Barriers such as vision, hearing and memory can affect eligible patients' interpretation of study material such as the patient invitation letter and information sheet. This is mainly an issue if the eligible patients are invited by letter or by phone rather than face to face. However, despite such barriers, some of these patients had agreed to participate in EQUAL. Although there was no difference between the two groups, this sub-theme observes that these difficulties can be barriers to participation.

4.3.5.2 Altruism and self-interest

4.3.5.2.1 Altruistic morals

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This theme captured the reasons most overtly motivating for individuals to participate in EQUAL study. Many of the interviewees conveyed altruistic morals which had driven them to take part in the EQUAL study or which they perceived as the most influential reason for taking part in research in general. For example, participant SAL_AGREE_08 commented:

*“I: So, you are a busy man with all your research participation?
R: Yeah well, I don’t mind you know I mean the treatment I’ve had off NHS because like I say, I’ve had my large bowel removed ...I’ve had sepsis, I’ve had diabetes, I’ve got arthritis but all this being looked after, so I have no complaints so I can put a bit back you know. If it helps somebody else later in life well why not? You know, somebody has obviously done it to help me you know. It is – well it is like anything else, isn’t it? You do not – you do not get to know – you cannot – you cannot advance knowledge without you doing these sorts of things.” SAL_AGREE_08*

The altruistic morals were along the lines of wanting to help benefit others, benefit the family, assist knowledge, and payback the National Health Service (NHS). In general, they aimed to help others with the illness, help the researchers to find a ‘cure’ or advance medical knowledge. Patients who agreed to participate in EQUAL often explained their decision with reference to altruism. However, the circumstances which motivated some individuals to agree to participate in EQUAL were very subjective.

The concept of altruism was less forthcoming in the interviews of the group that did not agree to participate. To illustrate this point, there were 37 quotes (17 participants) that were coded under the various sub-themes of altruism in the agreed group, In comparison only 13 quotes (11 participants) in the declined group. The declined group participants explained their decision not to participate in the face of altruism mainly as a result of the burden of medical illness, but a

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couple of participants expressed that they perceived no immediate benefit to them as a result of participation.

“R: Um, and I can, I know that it won’t help my case, but research has got to take place to help people in the future, I’m well aware of that, but I’m not just an ordinary kidney patient, I’ve got another problem as well you see, and I thought I couldn’t set myself up for all this.”
_BRL_DNA_13

“R: Well I really cannot see the point of it because (pause) if it is me personally, I have got something wrong and they were trying to help me, then go ahead and do it. I know it is for the future for other people as well, but, it does not actually help me, does it? At the time.”
_BRL_DNA_15

The altruistic moral of “help benefit others” was the most widely acknowledged, appearing in the accounts of nearly all (15/17) participants in the agreed group. This altruistic moral also had 77 quotes coded under it and was consistently expressed across the participant characteristics (age and comorbidity). The moral of “assist knowledge” was one of the other consistent reasons given for wanting to take part in EQUAL and captured reasons such as an intention to assist in the development of the knowledge base for healthcare professionals and thereby benefit future patients. The altruistic moral of “benefit family” captured the perceptions of participants who expressed that EQUAL participation would influence the medical care their family would receive should they go on to develop kidney disease in the future. The moral coded as “National Health Service (NHS)” captured the participant's gratitude for the care they had received from the NHS and a feeling they should or wanted to give something back in return. Table 4.6 summarises the various altruistic morals with illustrative quotations.

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Table 4.6: Altruistic morals and illustrative quotes

Altruistic moral	Illustrative quote
Help and benefit to others	<p><i>"I: And what did you think you would gain from [participation]it?</i></p> <p><i>R: Well I did not think medically, I would gain anything like that... It was just basically agreeing to make things better, perhaps, in the future." OXF_AGREE_02</i></p>
Benefit family	<p><i>"I: Once you read the letter, what did you think about it?</i></p> <p><i>R: Well I thought it would be a good thing, you know, it's not just me in the family it affected, it's, it was my sister as well (pause) and I've got loads of children, well grandchildren and great-grandchildren and that and so the, you know if anything can help that, plus helping anybody else if possible." OXF_AGREE_14</i></p>
Assist knowledge	<p><i>"I: What influenced your decision to say yes, to take part?</i></p> <p><i>R: Well because, I said, because research needs bodies and I mean, I am not in your field, but in engineering, we have a need to do research, is that piece of metal going to stand up to the load that I am going to put on it?" BRL_AGREE_01</i></p>
National Health Service(NHS)	<p><i>"I: So, when they came and asked you, how did you decide to say yes versus no? What made you say yes?</i></p> <p><i>R: Well, I think I have an interest and the fact that I have taken a fortune out of the NHS. If I could put that little bit back, it would make me feel better." SAL_AGREE_07</i></p>

4.3.5.2.2 Self-interest/Personal Gain

The converse of the theme of altruism is the theme of Self-interest/Personal Gain. Self-interest was an important feature that came out during interviews regarding patients' decision-making and motivation for research participation. This theme encoded the opposite of the feelings of altruism expressed under the theme of altruism (section 4.3.5.2.1). Ten of the 17 participants in the agreed group quoted self-interest as a reason for participation. The theme of altruism and self-interest often jointly emerged in the same interview, suggesting that they might be interconnected. However, Altruism was more potent with fifteen of

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the seventeen participants in the group that agreed to participate expressing this.

As illustrated by the quote below self-interest could have negatively influence participation.

“R: Well I really cannot see the point of it because (pause) if it is me personally, I have got something wrong and they were trying to help me, then go ahead and do it. I know it is for the future for other people as well, but, it does not actually help me, does it? At the time.”
_BRL_DNA_15

As illustrated in the following quote (BRL_AGREE_12) it is often difficult to disentangle altruism from self-interest and which of these is an overriding motivation for participation in research.

I: Were there any parts of the study that drove you to decide to participate?
R: No, no I never had that negative attitude at all. I was very keen on it because if my condition gets worse, I shall need all the research that’s done and all the progress they have made.” *BRL_AGREE_12*

The below quote made by BRL_AGREE_09 was less straightforward. Although this reads as self-interest, it is more inclined to altruism with a sense of pride the individual gets from being altruistic

“I: What prompted you to participate?
R: Well as I said to you in the very beginning really, I have, I am very keen, especially in the medical world, you come across anything that you can be of help. Years and years ago when I was a blood donor, they had the Anthony Nolan Trust, and they were getting, wanted extra blood for him, I straight away volunteered my blood, but unfortunately, it was not a match. However, um, I, I believe in helping if you can, and it does me no harm, and I feel I get a proudness really from being able to take part and maybe benefit other people in the future. That is my basic reason... I have always had an interest in health matters, and I feel that um, my input would be of use, would be, you know, I would be useful, I would not be a waste of time.”
BRL_AGREE_09

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In some instances, this was less straightforward. OXF_AGREE_02 felt that they had nothing to lose from participation. This is different compared to self-gain, and it is likely that they perceived participation to be low cost to them but not necessarily a benefit.

“I: What influenced you to say yes, to taking part?”

R: Well, I would not say influence, the point was, I was obviously having treatment for my kidneys, so just find out a little bit more, what was going on, you know? So, I mean there was no point in just ignoring it, you just go along with it, at least you can find out a bit more, and you have got nothing to lose, you know?” OXF_AGREE_02

Emphasising the importance of self-interest, a lack of perceived personal gain was a reason for non-participation.

“I: When you first got the letter (EQUAL invitation letter), how did you feel?”

R: (Long pause) Read like say half of it and thought “Oh well that is nothing to do with me, that is not really of any interest”. Not really interested, you know? Well, I really cannot see the point of it because if it is me personally, I have got something wrong and they were trying to help me, then go ahead and do it. I know it is for the future for other people as well, but, it does not actually help me, does it? At the time.” BRL_DNA_15

4.3.5.3 Convenience

Under the theme of convenience, a wide variety of sub-themes were noted, which were overall demotivating to participation in EQUAL. The theme was divided into caring responsibility, mobility, reliance on friends and family, home visits, transportation (driving and parking) and convenience issues while in hospital. Although the majority of the centres offered home visits, the perception of having to travel to hospital for the research study was a significant barrier to participation.

4.3.5.3.1 Caring responsibility

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Caring responsibility was an important issue to emerge from the interviews. This significant barrier to participation was elicited mainly in the declined group (7 vs 3 in the declined and agreed group respectively). This reason was also significantly expressed by the interviewees aged ≥ 75 years of age. (7 vs 3 in the ≥ 75 years vs 65-74 years of age respectively), but was quoted almost equally by women and men (6 vs 5).

I: When you were approached to take part in the EQUAL study you did mention that there was too much on at that time, would you mind elaborating?

R: Well I have got as I said my husband does not endure very good health, he is a diabetic, he is under the urinal clinic, he has had heart surgery, he is having problems even with his sugar levels at the moment, and I have to do a lot for him. I have to help him dress, I help him to wash, and it is all happening now. Up until this year, he was quite independent, so these sorts of things were all going through my mind.” BRL_DNA_09

R: Well as I say I can't go very far because of him, you know, I've got make sure he's ok, he fell in the greenhouse and we had to call the ambulance.... we don't go out very much now, we used to, but we don't go out now because he can't walk very far. He could not; he cannot walk from there to there without getting out of breath..... You see I do not have time really (Referring to participating in the EQUAL study), I know I'm here all the time, but I still don't have, and I can't just dart off and go there and go here, I've got to plan it, and I don't want to start doing that now.” BRL_DNA_14

The following quote was elicited from the son of one of the participants in the group that did not agree to participate in the EQUAL study. The son explained that the reason for non-participation was due to the poor state of health of his mother which was a result of the burden of the caring responsibilities.

I: So you read the letter, what did you think of the letter?

R: Well there was quite a lot to take in I think...

O: I think Mum ... in principle she would be up to do it. Maybe just medically she was not ...

O: My Dad, had dementia. Of course, she was trying to care for him as well, so I think the whole thing just got too much for her and I think

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it sort of triggered the sort of more rapid deterioration that was probably lurking in the background.” BRL_DNA_04

4.3.5.3.2 Mobility

Declining mobility is usually regarded to be a consequence of deteriorating health discussed in section 4.3.5.1. Healthcare related issues and patient activation. There appeared to be a link between self-reported mobility and participation status, those participating reporting better mobility. Fifteen of the seventeen participants in the group that declined to participate in EQUAL described mobility issues. In comparison in the agreed group, only seven of the seventeen had mobility issues. The eligibility criteria for EQUAL was the elderly (≥ 65 years of age) where the prevalence of mobility issues is likely to be higher.

I: And your mobility, how is that?

R: Not very good. I cannot walk very far.

I: And the times you must get to the clinic, how do you manage?

O: I, take him there.

R: It is dreadful.

O: to get him back in the car is an issue because of his legs; his legs will not bend.” BRL_DNA_10

One participant explicitly linked mobility to their decision whether or not to participate.

R: It is because, this, this is not to do with my kidneys; this is purely to do with the fact that I cannot balance.....and, I do feel very vulnerable. Moreover, that is frightening....Moreover, the fewer times I have to go out of that front door the better it is for me.....I know that it won't help my case, but research has got to take place to help people in the future, I'm well aware of that, but I'm not just an ordinary kidney patient, I've got another problem as well you see, and I thought I couldn't set myself up for all this. Because of my balance, I am frightened I will fall. If I fall and break an arm, I am in real serious trouble” BRL_DNA_13

4.3.5.3.3 Reliance on friends and family

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Patients in the group that did not agree to participate were overall more reliant on their family for support. This reliance was linked to reduced mobility, with ten of the fifteen patients who reported mobility as an issue also reporting increased reliance on friends and family. Although an explicit connection was not made between reliance on friends and family and non-participation, this was implicit in what the participants quoted during the interview. All of the patients in the group that agreed to participate who had mobility issues and expressed reliance on friends and family had expressed altruistic morals which had driven them to participate in EQUAL.

“R: I cannot... I have not got transport; I have a taxi. All my family is at work, and I do not want them to lose their job because they have got to have time off to take me somewhere. So I have a taxi from home down to the surgery, not far away but I have still got to have a taxi, and I have been going in for blood tests” OXF_DNA_06

“R: So, my son always, he’ll always take me anywhere if I wanted to go, but as I say, I don’t like to be a nuisance, so I don’t like to keep worrying people...it does limit you to what you can do, you know, you have to rely on people and you have to rely on transport to get you to the hospital” OXF_DNA_05

4.3.5.3.4 Home visits

Amongst those who agreed to participate, three said their decision had been swayed by being offered a home visit. However, in the group that did not agree to participate, 10 of the 12 who were asked this question felt that they would have agreed to take part in EQUAL had they been made aware of the option of home visits at the time of invitation.

“R: I thought I had enough problems getting up to the hospital for treatment. I did not want to have to go even more often than I already am.

I: Okay. If I were to tell you that as a part of the study, there is a facility to see you at home, or we only arrange to see you when you are attending a clinic appointment. Would that have swayed your decision?

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R: If you mean someone is coming here to interview me, then there is nothing wrong in that. My biggest complaint is that I would have to get out there and get out to the hospital, by one method or another and I find that difficult. You see, it is difficult to put into words.” BRL_DNA_13

4.3.5.3.5 Transportation

Issues relating to transportation were one of the most significant concerns and commented on by the majority of interviewees.

“I: So, when did you first come about to hear about this study called EQUAL?”

R: Well I think it was a lady is not it that came on the phone?

I: Yes.

R: And I said to her, what did it entail?... Going out there, and I thought Jesus, I cannot, I cannot, just cannot put up with this, it is enough to go out there when I have to go out there.” BRL_DNA_10

“I: How were you asked to take part in this EQUAL study?”

R: It was at the renal clinic, and one of the nurses came and asked me would I take part in it. Moreover, I said, “I will take part in anything as long as it is not a venue I have to get there too because I cannot get there.” SAL_AGREE_07

Patients in the group that agreed to participate had overall retained the independence of driving despite their co-morbidities compared to the declined group.

“I: Do you drive?”

R: Yes, yeah...the eyesight, after the cataract, has been pretty okay?” OXF_AGREE_04

“I: Do you drive?”

R: I am used to having a car and driving.

R: I have lost my car, I can no longer drive, I cannot get anywhere, so I am frustrated.” OXF_DNA_17

Parking in the hospital was quoted as an issue in a couple of interviews and related to the issue of participation.

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4.3.5.4 Help with decision

Interviews explored the process of decision-making. Family opinions and attitudes could have an overt influence on participants' decisions about whether to take part in the research. This could be either a positive or negative influence. The majority of patients who were approached to take part in the interviews in whom this theme was explored said that they had consulted with their family. (60%, 8 out of 14 in the agreed group and 7 out of 11 in the declined group). Of the eight in the agreed group who had discussed with the family, four had mutually decided to participate. In three cases the participants' the family had left the decision to them, while one had a positive influence.

“R: I spoke to my wife, and she said well, you do what you want to do. Did not consult anybody else other than that.” OXF_AGREE_03

“I: Was it a decision taken with your wife or would you have said yes regardless?”

O: We were there together, so I was there.

R: She had my arm up my back.” OXF_AGREE_17

“I: What did your family think of your decision to participate in the study?”

R: Nothing to do with them. It is my body.... I just tell them. I am the head of the family.” SAL_AGREE_06

Of the seven in the declined group who had discussed with their family, three had come to a mutual decision not to participate, three of the participants appeared to have had a negative influence from their family member and one had received a positive influence from the family but decided against participation due to other commitments.

R: I have got to say that my daughter in law who works in a hospital in the path labs and ugh she said mum do it, she said it is very advantageous if I go – it will help you a lot, and you are helping other

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people as well. So, she recommended me to proceed with it. However, there was so much going on” BRL_DNA_09

“I: So at the point that you received the letter, how did you approach it once you had read it? Did you discuss it with your other half, did you speak to anybody?

R: Well I showed it to wife ... I mean, you can remember reading it, can't you?

O: Yes.

R: As my wife said, at the time I was absolutely so overloaded with the hospital visits and blood tests and what have you.” OXF_DNA_01

“I: how did you come to a decision not to take part? Was it yours to make or did you speak to your son?

R: Well I mentioned to him, and you know, I said, this was something new.

O: From our point of view, I stood there as a neutral person saying, “Look Dad do you want to take part in this research or not?” You know at the end of the day it is something that one is not used to and for the reasons given etcetera, etcetera, privacy effectively you know, we declined.” OXF_DNA_12

4.3.5.5 Medical Research

This theme collated several sub-themes relating to participants' perceptions of medical research, such as the need for this, the importance of research and their previous experiences of participation in research (if any).

4.3.5.5.1 Perceptions of research

The attitude to research was positive in the group that agreed to participate in EQUAL.

“I: And what are your views on medical research?

R: Well they need to do that don't they to get to cure things, you know things what peoples got. It is like diabetes. I mean they try to get a cure for that but it will never be in my lifetime I should not think. ‘Cos I have had it since I was 20.” BRL_AGREE_10

BRL_AGREE_12 had a couple of family members who had died due to a congenital heart condition, and she owed the fact that she had lived up to the

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age of 65 years down to research and the improvement in healthcare that research had facilitated.

“my heart condition is inherited, as you know, and my father died at fifty, and my brother died at forty-two, and I am the only one out of three of us that have survived, and that is all down to research.”
BRL_AGREE_12

Altruistic morals (discussed in section 4.3.5.2) were strongly linked to participants perception of research.

“R: I believe in research. I believe in you know, there’s a way forward for, like there’s so much for cancer now, I mean we’ve all felt that one way and another, and I mean we can do so little, because we’re not in the medical field, but we have the benefits from all this.....if I can do one little thing, that is going to help the people with the knowledge and the know-how get to that place, in the end, we’re all responsible for that aren’t we. Everybody should be responsible for that. Cannot just leave it to the professors and the, can you, we have to chip in as well. So that is my reasons for being quite happy about research.....I have had much help over the years medically wise, and um, (clears throat) having lost family because it was not so advanced as it is for me, and have allowed me to live a longer life, I am all for research”
BRL_AGREE_12

Only three patients in the declined group felt that research was useful. The husband of OXF_DNA_17 had been recently diagnosed with Huntington’s, and her son was also the carrier of the gene. She was, therefore, hoping that a cure for Huntington’s would have been found before her son or grandson developing it.

“R: I do think medical research is important. I mean I am hoping the medical research will have done its wonders by the time my son’s or my grandchildren come to developing Huntington’s, I do not know.” _OXF_DNA_17

BRL_DNA_10 felt that research was essential for younger people, as they would benefit the most, but felt this was not the case for people of their age.

*I: what are your thoughts on research?
R: Well obviously it is a good thing, especially for probably younger people because they have got a chance of new things turning*

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up and helping them to keep their health. At my age, I do not expect anything is going to change any different, you know.” BRL_DNA_10

The majority of the participants in the declined group were neutral, and one expressed a negative feeling that research was a waste of time.

“I: what are your thoughts on medical research?

O: Well obviously, it is important to you people that are doing the work, but, we are really done, we are getting to the age where we have not got much patience, do you know what I mean? About things that do not really concern us, well we do not feel it does. My wife seems pretty good with her, her, kidney situation; it has not been getting any worse.” BRL_DNA_14

“I: what are your thoughts on medical research yourself?

R: I feel it is a waste of time.... I feel those people that are doing the surveys they could be doing a better job at looking after the patients.” OXF_DNA_06

4.3.5.5.2 Previous experience

This sub-theme captured interviewees past involvement in medical research or other activities promoting or related to research. Many of the interviewees who had agreed to participate in EQUAL had been involved with research in the past. Thirteen of the 15 participants in the agreed group, in whom this theme was discussed, were involved either directly in medical and non-medical research or activities similar to research such as questionnaires. In comparison, only two of the nine participants in the declined group had previously participated in research or similar activities.

The husband of participant *BRL_AGREE_10* said that although none of them had been involved in any research, they contributed actively to charities involved in research. These intentions suggested altruistic morals which had driven them to participate in EQUAL.

“M: I am all for it, to be honest, we do give to some certain charities...

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R: We give to too many.

M: British Heart Foundation....do the um cancer one in it, and I do the blind.

R: We do the Lifeboats.

M: Lifeboats. Foot and Mouth people, you know we've got certain other ones you know but I don't – I don't give every – I only choose two every month, pay monthly, the other ones I do as I you know I send a cheque off regularly you know, but we take it in turns more or less you know." BRL_AGREE_10

Several factors can have a bearing on the altruistic intent of participants – for example, where there may be an element of risk such as in a drug trial. Participant OXF_AGREE_17 expressed that a drug trial was something that they drew the line at. The interviewee had been invited to participate in a randomised control trial of sodium bicarbonate but chose not to take part as she was apprehensive of taking a new drug as it could potentially interact with the drugs she was already taking. She was, however, happy to take part in EQUAL which was a far less invasive observational study.

"I said 'basically that is a... I have just been looking for the information now', and I said, 'you do realise that I am high blood pressure, diabetic and some other things like you know, you put on a tablet, might happen'. I said 'I am already on medication, so everything is going quite nicely at the moment in time with my medication and everything. So, I do not want to take something that I do not need.'" OXF_AGREE_17

Only two of the participants in the declined group had previously taken part in research. Participant BRL_DNA_03 had previously taken part in a stroke study after his admission to hospital with a stroke. However, he refused to participate in EQUAL quoting that his mobility was not the same anymore.

"I: The stroke study you took part in it for two years and then the study ended, is that correct?"

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R: It was the end of the story, really, you know. They said that you would not be getting a final report because there is not one, you know what I mean, outside of the ... that the tests were being withdrawn.

I: And did that have a bearing on your general feeling of what research meant?

R: What, a negative feeling?

R: No. I mean, the only reason I am not particularly interested in doing the renal one is that you know, a lot of my time is taken up with my other medical issues, you know.” BRL_DNA_03

4.3.5.5.3 Worthwhile

A key factor when deciding whether to take part in a research study is whether the individual feels that the study itself is of value. For example, for BRL_AGREE_09, the potential value of the research was the primary motivating influence:

“I: Do you know what it (EQUAL study) involves for the future and how long you are going to be participating?

R: I know it could be a matter of three or four years or so, or even more, as long as I am alive and obviously can still talk to people, I would be happy for, for it to continue. Yes, I would, I am quite happy with that. Because, as I say I think it is a very good, worthwhile thing that you are doing, and I agree with it, totally and I wish that more could be done for so many more problems, you know.” BRL_AGREE_09

4.3.5.6 Personal and beliefs

This theme explored how participant life experiences, personal characteristics and beliefs may have motivated research participation.

4.3.5.6.1 Early life

Five of the seven participants in the agreed group had displayed a humanitarian, giving personality since early in life or had worked for the national health service, which was influential in them agreeing to participate in research. In the group that did not agree to participate there was no such evidence demonstrated in their early life through the interviews.

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“R: I am a widow now, We had four children, and then we had, we fostered four, this one here, (girl’s name) she died when she was thirty.” OXF_AGREE_14

“I had given blood from when I was old enough at eighteen to start, to help other people and it has just carried on that (pause) any survey that’s been necessary or I thought would be helpful to other people; I have contributed to it, you know.” OXF_AGREE_17

4.3.5.6.2 Family and Friends’ health experiences

Several of the participants (ten) in the agreed group in comparison to three in the declined group, had witnessed their close family members experience significant adverse health conditions including kidney disease, which could have influenced their decision to take part in medical research(EQUAL) though they did not make this explicit connection.

OXF_AGREE_14, quoted the various health experiences of her family, initially referring to one of her foster daughters and then her sister followed by her husband.

“This one here, (girl’s name) she died when she was thirty. Down in Bristol, she had a bad heart. I had a sister, I had two sisters, but the eldest one of those died through, with this same kidney condition sort of thing. My husband um, had diabetes, he must have had it for years before it was ever picked up. He had part of one foot amputated and then he had, uh, the other one below the knee amputated. Moreover, then it was, uh, oh diabetes infecting it and he went totally blind, um, all that sort of thing and when we were at the hospital once, he, when he was getting really poorly, the consultant there said about dialysis for him” OXF_AGREE_14

SAL_AGREE_08 is referring to his brother-in-law commented that people are more willing to participate in research when they are desperate. This could be a potential explanation of why cancer research is eliciting better participation than research in other fields.

R: “.....sometimes you are prepared to try it out because you are on death's door, like my brother-in-law, he is dying with cancer you know,

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and he is quite happy to try things out which you know you would do wouldn't you? SAL_AGREE_08

Participants in the group that did not agree to participate had also had close family members experience health issues. However, when compared to the agreed group, this group had other mitigating circumstances for declining to take part in EQUAL. For instance, for the agreed group their family health experiences had driven them to participate in research (EQUAL) whereas for the group that had refused participation in EQUAL the experiences might have had the opposite effect and made them averse to anything remotely connected with healthcare.

For example, OXF_DNA_05's wife had died of oesophageal cancer a few months before having received the invitation to participate in EQUAL. Over the years of his wife's illness, they had moved away from medically related discussions. Although this was not overtly expressed, this could have influenced the decision not to participate.

"She had cancer of the oesophagus, which she was treated for and she lived for another 20 years, and after that, when she cleared of having that cancer, she lost one of her breasts. So in a way, all that she had been through, she would not even watch hospital things on the television, you know, it sort of, she did not talk about it. It might be mentioned, but that was it, we never went into deep discussions over anything like that." OXF_DNA_05

4.3.5.6.3 Proactive

This sub-theme captured the participants' eagerness with regards to healthcare related issues and overall decision making. It is probably unsurprising that the participants' in the agreed group were overall more proactive.

"R: I mean; in fact, they would not have needed to tell me why they picked me. So, long as I knew it was something relating to my health. Like I say, I have attended two seminars....I would not have attended them if I'd not been interested in my health and what is being done

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about it and what is new on the market because every time there is one we go. Well, every time you learn something new.” SAL_AGREE_05

4.3.5.6.4 Mindset

The interviewees who had agreed to participate in EQUAL overall had a very positive outlook towards life despite their illness and co-morbidities compared to the EQUAL non-participants. This reflected in their enthusiasm to participate in research. The declined participants were overall more overwhelmed with their health care related issues.

“R: I know that it won’t help my case, but research has got to take place to help people in the future, I’m well aware of that, but I’m not just an ordinary kidney patient, I’ve got another problem as well you see, and I thought I couldn’t set myself up for all this.... not because I didn’t want to help, but it’s just that it’s me, my situation is different from other people’s..... Because if I fall and break an arm, I am done for.... I am not dizzy, but I am unstable.....And that is frightening..... And the fewer times I have to out of that front door the better it is for me.” BRL_DNA_13

4.6.4.6.5 Privacy

Only one interviewee commented about privacy and quoted this as an issue for non-participation. The son felt that his father was a very private person and that this was one of the main reasons for not participating in the study.

*“ I: And what are the reasons for you not to take part?
Q: I mean to sum it all up; it is down to privacy at the end of the day.”
SON-OXF_DNA_12*

4.3.5.7 Study-related

Under the broader theme of ‘Study-related’, a wide variety of subthemes, or categories, were noted. These were: why chosen, study understanding, reaction to the invitation, the experience of renal unit, manner and method of approach and clarity of invitation/information.

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4.3.5.7.1 Why chosen

This sub-theme was mainly descriptive and collated participants' perception of why they were chosen. Nine of the 13 participants in the agreed group and nine of the ten participants in the declined group were not aware of the reason why they had been invited to join in the EQUAL study.

Not aware

The patients were not aware of the fundamental reason behind why they were invited to participate in EQUAL and the reasons behind what made them eligible.

*"I: Do you know why specifically you were being asked to take part?
R: No, I just thought I was just one of the millions if you like."
BRL_AGREE_01*

*"I: And did they tell you why they had asked you to take part? Why you specifically?
R: It was when you get to a certain age, and you have problems, and they are doing a study that can help people in the future. It is no use to me now, but it will help other people." SAL_AGREE_07*

BRL_DNA_15 felt that they were not relevant to the study.

*I: Okay. Um, when you first got the letter, how did you feel? When you looked at it?
R: Read like say half of it and thought "Oh well that is nothing to do with me, that is not really of any interest". Not really interested, you know? BRL_DNA_15*

Aware

Some of the participants in the aware group had only a vague understanding of why they had been chosen to participate.

*"I: And do you know why they asked you particularly, to take part?
R: I think it is just because of the chronic kidney function." "I am just wondering whether they did not actually say, I am not sure whether it would have been an age thing or not, whether they were taking it."
OXF_AGREE_02*

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I: How did you first come to hear about the study that you are taking part in?

*R: "Saying my name was flashed up because I was the right sort of age and the right level, with the bloods or whatever it is."
OXF_AGREE_14*

4.3.5.7.2 Study understanding

This sub-theme again was mainly descriptive and captured the participants understanding regarding what participating in the study entailed. Nine of the 17 participants in the group that agreed to participate had no understanding, six were partly aware and only 2, fully aware.

I: And was it clear to you why this specific study was being done?

R: Only in so much that you need the information to probably change things, from what is already in the public domain at the moment." BRL_AGREE_01

I: Okay. Now, having read all the information that you were given, was it immediately clear to you what was going to happen for the duration of the study?

R: Not really, no. Well, it is that long since I read it, to be honest, you know.....

R: You read something, you forget it, you know.

I: But having refreshed your memory now.....

I: About what was going to happen for the study? How long you are going to be followed up, things like that?

R: No, that does not bother me because as I say I've done similar studies." OXF_AGREE_17

One participant said that she was aware of what participating in the EQUAL study meant but on probing further became upset. She was unable to differentiate between her routine clinic visits and visits relating to the study and was not aware that she was participating in EQUAL.

I: And having read it was it clear to you what was going to happen once you agreed to take part in this study?

R: Yeah more or less yeah.

I: What it would entail, what would happen at each step of the study - that is what I meant.

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R: Do you think it is worth me doing it? Because I am not very helpful.”

“I: Have you, had to take extra blood tests or have you had to complete questionnaires?

R: Right when I go to the clinic first thing they do is um got to be weighed, and ugh take my urine and then ugh I get to go and have my blood took, and then I go in to see the doctor.”

I: Oh, I was more talking about the study.

M: But basically, in the study, this is as far as you have done as we are concerned, they have not asked anything apart from that.”

“I: Have you filled out any questionnaires?

M: Ugh which questionnaires – I cannot remember we got. Which questionnaires was it?

I: Questionnaires that asked about the questions relating to how you are feeling, about your physical health and things like-

R: No.

M: I think so well yeah

R: I cannot – I have had so many forms.” BRL_AGREE_10

One of the participants who had agreed to participate had limited awareness of what participating in the study meant but had a poor understanding regarding the relevance of the study to their current illness. This issue also relates to limited awareness of the renal condition which is discussed in section 4.3.5.1.3 above.

“ Well I did say to nurse X when she came after the first and left me with this thing to go through and I said to her, course a lot of this the answers or the questions here, really don't apply to me because this is uh, questions for people who are really suffering because of kidney problems failure and then they were talking about how would you feel about dialysis and things like that, so well I said to nurse X “the thing is I'm not that advanced” so you understand a lot of the questions were for people who were on their way into dialysis really, so I said to her “there are, there are quite a few questions here that don't apply to me at all.” BRL_AGREE_12

It is noteworthy that although some participants did not have much awareness, this did not deter them from participation.

“I: having read this was it clear to you what was going to happen throughout the study? Did you have any questions?

R: No, I suppose not. Um, I was not bothered about all this information goes here, there and everywhere, because that is the whole intention and it

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does not matter if my name came into it, I am not bothered about that. However, I am interested in the results at the end of it.”

“I: What they are actually hoping to achieve?”

R: No, I really do not. I do not know whether, well, I do not know research seems to involve many things, does not it. I suppose. I do not know; I do not really know an awful lot about kidneys, I was actually in hospital with a young lady who actually put herself on dialysis, I know it is to do with the waste product and everything like that, but I do not really even know whereabouts it is. I’m a bit silly like that; I do not get too serious about it.”

BRL_AGREE_12

Of the 17 patients in the declined group, 16 were asked the question relating to study understanding, 13 had no understanding of what the EQUAL study involved with only 3 participants being partially aware of what taking part in EQUAL meant. This would suggest that understanding of study purpose was lesser compared to the agreed group and could have had an influence on participation. This accurately reflected the patient understanding of EQUAL as the interviews were conducted fairly soon after they had agreed or declined to participate in EQUAL (time of decision-making).

“I: What did you hear about the EQUAL study?”

R: I know nothing about it at all. I do not know what it is all about.

R: I can imagine sitting just in a room talking about it; that is all.”

BRL_DNA_14

4.3.5.7.3 Reaction to invitation

Included under the umbrella of this theme were questions intending to explore patient’s reactions to an invitation to the EQUAL study. Overall, participants from the agreed group did not express much of a surprise about the invitation, and one participant (SAL_AGREE_07) was ‘thrilled’ that she was invited to take part. However, participants in the ‘did not agree’ group expressed a sense of shock, disbelief and felt overwhelmed that they were being asked to take part. This could be related to the timing of the approach discussed in section 4.6.4.6.6.

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SAL_AGREE_07 was happy that she was invited. She felt indebted to the NHS due to the care she had received over the years and also understood the purpose of research. She had developed myeloma and had been offered thalidomide as a trial, and that cured her of the disease.

“R: It might not seem much to some people, but I was thrilled to bits when I was asked.” SAL_AGREE_07

4.3.5.7.4 Manner and method of approach

Across most centres, all eligible patients were invited to take part in EQUAL via an invitation letter and information sheet sent in the post. This was then followed up with a phone call to confirm whether they were willing to participate.

Six participants in the agreed group felt that the friendly method of invitation had a role to play in the decision to participate in EQUAL.

“I: What was, what was good about the way she went about asking you to take part? What is it that appealed to you the most?”

R: That her mannerism was very good, you did not, you felt at ease all the time, there was, she said if there are questions you do not want to answer, do not answer, she said, I quite understand, so yeah” OXF_AGREE_03

The majority of the participants both in the agreed and did not agree group did not remember getting the letter; one must, however, bear in mind that the qualitative interviews were conducted a few weeks or on occasions, a couple of months after the invitation to participate in EQUAL had been made.

I: Did you remember getting this letter? Do you remember reading it?

I: I show it to you. Does that ring a bell?

R: Well I think I have had one like that, but I do not think I read it all because it is such a lot to read, and my eyesight is not quite so good as it used to be, and um it takes me a long time to read anything nowadays. BRL_AGREE_10

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The majority of the participants in the agreed group felt that it did not matter how they were approached though they preferred the approach to be face-to-face. Five of the seventeen participants in the declined group felt that a telephone call might not have been the best method of establishing contact. A few felt that they were often harassed with cold calls from salesman over the phone and therefore a telephone invitation would put them off. This could prevent them from engaging in further conversation. Had they been invited face-to-face this would have influenced their decision to participate. Inviting participants to take part in the qualitative sub-study at times proved to be a challenge as I was frequently mistaken to be a salesman.

“O: And of course, the other problem is, with the old people, is you get so many, you know, bogus callers and of course, at the end of the day, she picks up the phone and if she hears somebody she doesn't recognize and she thinks, “Oh, well, that's not family, and it's not the doctor or something – I don't wanna ...” you know, so it's almost not giving the person who's trying to make the phone call, to make the communication ... giving them a chance to say something, you see, and probably also not quite understanding what it is all about.” Son of BRL_DNA_04

“R: Well, for me, not forms, make a contact that I can respond immediately to that question. When paper lands on my desk, being in business, I get lots of paper, you know, and at that specific time, I might be too busy, you know, because other things are falling about my ears, and I have got to answer someone else.

I: Sure, but I think, so personally you feel a personal contact would work better for you?

R: For me, yeah.” BRL_AGREE_01

“R: Well, I only heard about this one when actual fact the young woman phoned me up.....What happened in actual fact, if I am doing something like this I prefer to sit in front of somebody so if I have a problem I can ask a question SAL_AGREE_05

4.6.4.6.6 Timing of approach

The timing of the approach was one of the key factors that influenced the decision of whether to participate in EQUAL or not. In at least half of the participants who

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had declined to participate in EQUAL, the invitation had come at an inappropriate time usually when the patient was unwell.

For example, BRL_DNA_03 had been approached at a time when their illness was accelerating. Regardless of the patient's perceptions of the research, this overruled any thoughts regarding participation.

I: What did you think of the way the lady that called you asked you to take part in the study?

R: It was just a polite follow-up to her letter,I had just been told that I would probably be going on dialysis then, and I thought ... well, it was not a matter of, "No, I am not doing it – it is a waste of time." It was a matter of, "Hang on, I am starting to get a little bit ill, and I would like to know how it is going and what is happening before I take on any other commitments for the hospital." BRL_DNA_03

I: Okay. So, when did you first come about to hear about this study called EQUAL?

R: I do not really know, it is just, I say it caught me at a wrong time

O: If we declined it though I think at the time he was probably so poorly we did not want to do it." BRL_DNA_10

Illness experience in the family could also contribute to it being the wrong time to be approached (section 4.3.5.6.2)

R: Well last year was a very bad year, I discovered my husband had Huntington's disease, um, I had to leave my home he had to go into a care home, and then I came down here, which was all very traumatic." OXF_DNA_17

4.3.5.7.5 Clarity of invitation/information

The wife of a participant (BRL_DNA_10) who had not agreed to participate in EQUAL felt that the letters had to be more explicit. Her husband who had developed a general aversion to hospitals as a result of a previous experience refused to participate in EQUAL after seeing the letter with the hospital's name on it and therefore assumed that participation would result in increased visits to the hospital.

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*“I: Now coming back to the study itself and the way we invited you, what do you think was good or bad, what could we have done better?
O: I think they need shorter letters.
O: And maybe make it more explicit. That it could be done in your home. I think people like him would just see the word [hospital name]
” BRL_DNA_10*

On the other hand, a daughter (BRL_AGREE_12) felt that the invitation letter was well laid out.

*R: It [information sheet] is quite clear, you know, what the purpose is and how you were approached and whether you want to or not.
I: But, did you think in any way it was elaborate or sufficient?
R: I’ll tell you, my daughter was here when (clears throat) I was reading this because she, the field she is in, she is trying to make all this kind of thing, even a prescription, understandable for people with Alzheimer’s, DSA and that, and so actually she, she’s still got it.”
BRL_AGREE_12*

On any of the study materials, it is mandatory to have the details of the lead site/sponsor of the study. One of the participants who agreed to participate in EQUAL felt initially a bit panicked at the thought of having to drive down to Bristol from Oxford for the study visits.

*“I: When you received the letter did anything go through your mind? was there anything that you thought about, or you just said, fine yes go ahead?
R: I did when I first read the, uh, I thought oh blimey going all the way down to Bristol and that. Moreover, then I asked Nurse J about it, no she said uh, it would all be done here.”
OXF_AGREE_16*

4.3.5.8 Trust

Sub-themes that were explored under the umbrella of trust were the source of contact, confidence in approaching the person, and privacy.

4.3.5.8.1 Source of contact

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Patients that were eligible to participate in EQUAL were contacted by research nurses. Thirteen of the 14 participants in the agreed group had no strong feelings on who had contacted them and felt that this did not affect the outcome of their decision.

Interestingly a great many in the group that did not agree to participate said they would have strongly considered participation had their current physician posed the question, with six of the ten interviewees or partners of interviewees who refused to participate in the EQUAL study expressing this. Interpersonal trust-in-physician was linked with the desire for participation. This suggests that the trust built over time in the physician-patient relationship has a role in the participants' decision-making process. The participants felt that they shared a relationship with their physician and they described them to be "good", "nice" and said they had "every faith in them" and hence would have agreed to participate.

"I: On the other hand say if the consultant you see in the kidney clinic, if he had said there is a study that's going on, would you take part? What would your response be?"

O: I think we would have done anything because we have got every faith in him."SPOUSE-OXF_DNA_16

One spouse commented:

"I think if Dr X ... she gets on quite well with him, actually. If he had asked her on one of his visits and said, "Look, we are gonna do this research, you know – would you, do it?" I think that would have made a big difference. I think that would have ... she would have said, "Oh, yes, okay, it is fine. " Because, you know, you build up a relationship with ... sometimes ... obviously, you do not see the same specialist all the time, but you do build up ... you know, even though you are only seeing him for five minutes, it is surprising how you do get this sort of thing going. It is a confidence thing I suppose." SPOUSE-BRL_DNA_04

It was important for a few others that the contact had originated from a trusted source which was to them the renal clinic.

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“The renal unit, I see. I have found up there um, it is a different situation than the cardiology where I go, it is um, very friendly..... However, I have found the staff so very different than they are in cardiology. They are very helpful and very, they seem to care more about you yourself, you know? Yes, and a good atmosphere, my partner always says that a good atmosphere in here isn't it? I said “Yeah”.” BRL_AGREE_12

In one instance, one of the interviewees had both good and bad experiences with the medical fraternity. Both the participant and their spouse felt that who invited the individual to participate in research was key to whether they agreed to participate.

O: If it were the doctor you see about your eyes you would have said no straightaway, he was absolutely obnoxious.

I: So, it depends ... are you saying it depends on the person?

R: Definitely, it would be that because half of them medical doctors are obnoxious, like the one we saw about me eyes. “ I see Dr W; you could talk to him like a man to man type thing.... However, no problem at all with Dr W.....it (agreement to research participation) comes down to your comfort zone with the doctor.” SAL_DNA_02

4.3.5.8.2 Confidence in the approaching person

This sub-theme captures the views of the agreed participants and the factor that had influenced them to participate in EQUAL. The declined group did not comment on the character and skills of the person who approached them.

The consensus was that the inviting person should be able to appropriately answer any potential queries.

“.....It is no good trying to persuade someone to um take part in something if you cannot give them sort of honest answers to questions. Moreover, uh, therefore it is got to be a knowledgeable person to, be putting the study forward and in the same way, people who are sensible enough to be able to answer and um take part in the study. However, no, I think, a nurse, if she is qualified if she has the qualifications, there is no reason why a nurse or a doctor or whatever other um, comes in between those two could um put forward this study.” BRL_AGREE_09

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Participant BRL_AGREE_11 was more than happy to be approached by a nurse and regardless of the person approaching he felt that a casual manner was what appealed to him.

“I: What the person inviting you made a difference to whether you participated or not?”

Well, it might have done, if there was someone there in a white coat and a surgical hat on (laughs)... however, no it is done in a, in a casual manner and as far as I am concerned that was the way to do it. Basically, if you go in and see a doctor in a white coat and there are nurses in blue or whatever they have got now, it is purely formal. When it is informal, it puts you at ease.” BRL_AGREE_11

4.4 Discussion

4.4.1 Main Findings

When interview data were analysed, all the patients were found to have expressed motivations and barriers for their participation. The different context of the interviews (agreed and decliners) might have had a bearing on the kind of topics that emerged from the participant's accounts. These fell into seven key themes: altruism and self-interest; convenience; help with the decision; medical research; personal and beliefs; study related, and trust. Additionally, a descriptive category of healthcare-related and patient activation emerged, which indicated differences between the agreed and declined group. What is of most importance is that the findings of this study are the personal feelings of those older adults who agreed or declined participation, in clinical research and they give an indication of the circumstances which influence their decisions during recruitment and ongoing participation. In the qualitative data the key issues that arose were:

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1. There was no significant difference in the themes by site (high, medium and low recruiting sites) and the recruitment rates were more likely related to resources and competing studies.
2. The theme of convenience was overall demotivating to participation in EQUAL, with caring responsibilities and transportation difficulties being particularly discouraging to participation in the EQUAL eligible cohort.
3. Patients who engaged with their healthcare and who were more activated were more likely to agree to participate in research.
4. Altruistic morals had a strong influence which had driven them to take part in the EQUAL study. These altruistic morals were also strongly linked to participants' perception of research. However, the relationship was complicated as all of these patients had also expressed altruistic morals which suggested that self-interest could be a prerequisite for altruism.
5. Interpersonal trust-in-physician was strongly linked with the desire for participation.
6. The agreed group overall had a very positive outlook towards life despite their illness and co-morbidities compared to the declined group which reflected in their enthusiasm to participate in research.
7. A majority of participants in the agreed group and the declined group were not aware of the reason why they had been invited to join in the EQUAL study.

4.4.2 Relationship to literature

A considerable amount of time, effort and often resources are spent on recruitment into research with varying rates of success. It is imperative to gain an understanding of the reasons why individuals choose to participate or otherwise in research. Mapstone et al. attempted to identify reasons behind why many research

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projects fail to recruit their targeted numbers. (333) Patients' inclination to take part in research studies is probably to be prejudiced not only by the study design but also their perception to research. Numerous issues and several barriers to research participation have previously been widely studied by both quantitative and qualitative studies to date (260, 334, 349-352). Several articles have even specifically looked at the issues of motivation and deterrents to participation within a population of older adults (269, 353-356), but there is a distinct lack of studies that have attempted to investigate the experience of a range of older adults who had participated in the research. The unique aspect of this qualitative study is that it captures the motivation and barriers of older adults for participation in research. Another fascinating feature of this study is that it not only captures the experience of and reasons behind participation of the agreed group but also aimed to gain insight into the deterrents and barriers to participation in the declined group who were invited to participate in EQUAL. Patients who have declined to research are often a difficult group to gain access to but it essential to include their experiences if we are to improve recruitment and improve the validity of a study.

The target population of the EQUAL study was different. They were not only older adults, but all had advanced chronic kidney disease. They also had other issues either resulting from their kidney disease or because of co-morbidities such as diabetes. Therefore, the themes and issues that have emerged from this qualitative study are novel and can translate to research involving older people and other chronic diseases. These issues must be considered in the planning of future research studies involving the elderly.

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It is difficult to adequately assess how the participants of this study compare to the general population of research subjects (generalisability) with regards to age (elderly) and co-morbidity. Several authors note that older adults, in particular, are consistently underrepresented in clinical trials and studies. (278, 357) This gap is viewed as a significant disadvantage for the ageing population as the evidence of clinical research does not apply to them. (267)

It should also be expected that most chronic conditions are likely to produce some of the complications mentioned above, especially in older adults. As a result of the issues that go with multi-morbidity and age, the risk-benefit ratio of clinical research participation is always considered both by researchers and participants. The risk-benefit matters drive the decision making, and where possible, patients should be permitted to take part in any research they are willing to. (358)

Several assumptions are commonly made about older adults which prove detrimental to their participation in clinical research. (267, 359, 360) These assumptions may be seen as ageism. The literature reveals a perception among some clinicians that their older patients are vulnerable and unable to make informed decisions for themselves: such a 'protective' clinical paternalism can be a barrier to the inclusion of older individuals. An expectation of the UK Government is that older adults should be more "... proactive and participate in decisions about their care."(361)

Research by Levy et al. also found that older adults were more likely to participate in clinical research studies when convenient for them, for example, regarding location. (271) Although EQUAL offered home visits in most centres, the notion of research studies being associated with the hospital and the concern of getting to

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the hospital was a barrier to EQUAL participation. The potential of home visits could have also been better communicated with the patients. This was rectified in the patient invitation letter by submitting a minor amendment. To overcome this barrier recruitment policy can be better shaped to recognise that older adult study participants are more likely to participate in medical research if the possibility of home visits is highlighted during the invitation. One of the unique elements elicited from the interviews was the aspect of caring responsibilities that were a barrier to participation. There is a minimal acknowledgement of this in the literature. (362) This barrier may also be addressed by offering home study visits in any research involving the elderly.

Further, the availability of transportation was a critical issue, especially for those who had stopped driving or were widowed. It was a consistent topic of this study, and many of the participants reported that had there not been home visits then they would have been unable to take part. This is an important issue to consider when designing a study with older adults and budgeting for transport and home visits could aid recruitment.

The chronic illness care model emphasises patient-oriented care, with patients and their families integrated as members of the care team. (363) Patient activation can be measured using the Patient Activation Measure (PAM) and is defined as the patients' knowledge, skills, confidence and ability to take an active role in their health care. (364, 365) Patient activation has been shown to have an impact on the patient-assessed quality of chronic illness care. (366, 367) Improved patient activation has also been shown to improve patients self-management behaviours. (368) Therefore it is highly likely that patient activation has a role to play in patient engagement and participation in research. In this study, the agreed group

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were overall more activated, being more forthcoming about health concerns not directly relating to the consultation, more aware of their medical condition (including the cause of their kidney failure) and would promptly consult their general practitioner in comparison with the declined group.

This study has also shown that frailty, which could be a marker of co-morbidity, could have been a barrier to research participation. Patient frailty impacted on their mobility and this, in turn, made them more reliant on their family and friends. Ridda et al. in their study used the frailty index as a tool to measure frailty and to document barriers to recruitment. (268) In the above study, only 39% of potentially eligible patients who were approached agreed to participate.

In general, altruism (334, 369-373) and self-interest (369, 371-376) are frequently quoted to be vital in influencing inclination to participate in any research studies. Altruism is defined as “disinterested or selfless concern for the well-being of others”.(377) Altruism has been emphasised as an important and apt motivator for individuals to enrol in research, with an argument that clinical trials are more ethical when participants act out of altruism instead of self-interest (334, 369, 370, 372, 373). The majority of the patients in the agreed group expressed altruistic morals which had driven them to participate in the EQUAL study, and this was a recurrent impetus expressed by the majority of the interviewees during the interview. Their altruistic belief seemed to be grounded on the belief that research studies would improve medical knowledge, improve treatments, ‘find a cure’ and ultimately ‘benefit others’. However, this was less forthcoming in the interviews in the group that did not agree to participate. An issue that was evident in this study was the personal sense of good that the participants felt they derived

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from being able to participate in a study which could improve healthcare for others in the future. This was in line with the findings in the literature. (360)

The motivating themes for participation also included self-interest and personal gain. Some studies argue that self-interest is a stronger reason for participation than altruism. (378, 379) In this study on some occasions, it was difficult to disentangle altruism from self-interest and which of these was the overriding motivation for participation. The quotes suggested that the relationships were more complicated with self-interest often a prerequisite for altruism. Preserving a 'net personal gain' and safeguarding their self-interest were found to be significant factors in promoting research participation. The self-interest in this study was governed by knowing more about their condition and being able to participate in finding a cure for the condition (kidney disease). If the participant invited to take part in research feels that they are participating in research that is worthwhile, it is more likely that they will have a positive experience. (360, 379). This was in line with the findings of Alexander et al. who noted that: "...Literature has provided strong evidence that research among vulnerable populations may not be harm-free but may also be of direct benefit to participants".(360) Benevolence, and the ability to be significantly useful to society are their own rewards. Morrow-Howell, Hong & Tang investigated the personal benefits to volunteers. (380) They found that there was inconsistency as to whether specific groups of people benefit from volunteering more than others. They did, however, report some evidence which suggests that those individuals who are disadvantaged regarding personal and social resources, experience more positive outcomes. A variety of backgrounds and lifestyles were represented by the participants in this study, but the interviews did not explore in depth the difference in the benefits felt by any of the

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participants. Future qualitative studies should investigate in-depth the effects of socioeconomic status on the benefits perceived by volunteering or participating.

Another important issue noted in the study was that interpersonal trust in the physician could potentially have an important role in the participants' decision-making process. Also, it was also down to the confidence in the source, e.g., The Renal Unit and the qualities of the recruiter and sense of confidence in the person approaching them rather than the Nephrologist themselves. Adams et al. carried out a comparison of different recruitment methods to a clinical trial and found that the highest yield of participants came from direct presentations. They considered that this was due to the high level of trust exhibited by patients toward their physician and other caregivers. (381) Equally, a few studies have claimed that there is a prevalence of mistrust of health care in general and research projects in particular among older patients.(359, 381, 382) However, none of the authors expands upon this or speculates why this may be. None of the interviewees was introduced to EQUAL by their Nephrologist. It has been noted that health care providers, including doctors, play a critical role in recruitment because they often introduce the option of research to patients. (359) This can be an important strategy to improve recruitment in research, but there is always a fine balance between introducing research and the ethical issue of coercing patients to participate in research. Although there is a general belief that doctors are more successful at recruiting research participants than nurses, Donovan et al. found no significant difference in recruitment rates between doctors (urology consultants) and nurses for prostate cancer-related RCT. They also suggested that nurses were more cost-effective recruiters, despite spending longer on average with each patient. (383)

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In this study, the participants voiced a preference for the initial contact to be in person in a clinic as opposed to it being in writing which could be related to the issue of trust. This is in line with findings reported by Tolmie. Et al. (354)

Several authors have also indicated that, when invited to do so, older adults are generally not only agreeable but also have a positive approach to taking part in clinical trials and research (267, 384, 385). However, this study indicates that this willingness is often dependent upon the research process providing flexibility toward appointments and procedures. It is important to recognise that the fostering and maintenance of a relationship of trust are essential throughout the recruitment and retention of participants.

Lovato *et al.* (1997) found that recruitment amongst the older population was not any more difficult than amongst individuals of any other age group, with participant refusal rates for trials in this segment of the population appearing like those in trials carried out primarily with other age groups. (260) This, however, goes against the findings of Gonzalez *et al.* who suggest that it proves to be: "...difficult, time-consuming and expensive"(273). While some retired individuals may have an abundance of time available, many healthy seniors either continue to work or have very active social lives with many time commitments as demonstrated by some participants in this study. If the investigators can coordinate their hospital appointments to research visit appointments, then the participants find it easier to participate.

Finally, a unique finding of this research, not previously recognised in the literature, is that older adults may lack exact awareness of the reason why they have been invited to join a research study and what participation will entail. However, some studies have acknowledged this in other age groups as a product

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of insufficient information given to the patients' from the recruiters. (386) This is likely to be because of ageing but may also be a result of their co-morbidity burden including dementia. Therefore, some consideration and thought should be given regarding the ethics and process of invitation to research participation for elderly and multi-comorbid patients. A way to overcome this issue and in the process optimise recruitment and retention is a to train the recruiters to make sure they communicate the study effectively, face to face rather than via postal recruitment (since some participants experienced difficulty in being able to read recruitment materials due to visual or other impairments), that they involve carers and family, send reminders or newsletters and provide a contact helpline to allow patients to communicate with research nurses.(386)

4.4.3 Strengths and Limitations

This study sampled the views of several individuals over the age of 65 who had taken part or declined to take part, in EQUAL. Although not explicitly discussed in detail within the study, it included individuals from a variety of diverse current health statuses but did not explore the influences of socio-economic backgrounds and research participation. Although anecdotally in the interviews of those that did not agree to participate, interviewees were of low socio-economic status. It would have been useful to capture the perspectives of patients who dropped out of EQUAL as high patient drop out affects the study's validity. Also, interviews of the research teams (research nurses) would have given insight into how centre priorities could potentially influence recruitment to a study.

This study is unique as it may be the first to qualitatively study the perceptions of a group of patients who are not only elderly but also multi-morbid. The study explored a wide variety of issues and has yielded valuable insights on a breath of

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topics. The study was not restricted to a specific region and explored barriers and facilitators across three of the EQUAL sites. A good understanding was achieved by a large group (N=34) of both the agreed and declined groups (16 in each group). One of the strengths of this study is the capturing of views expressed by those who had declined research participation. Typically, the voices of such individuals are not heard. Their accounts were compared and contrasted to those of patients who had agreed to participate. This study has therefore added significant value to the sparse literature which has explored the perspective of study decliners and reasons for non-participation. (387, 388).

4.4.4 Recommendations

Several recommendations for improving future practice and inclusion follow from the findings of this study:

1. Recruiters should not adopt the same recruitment strategies for all demographic groups.
2. As far as possible, investigators should be aware of the potential motivations and barriers to the recruitment and retention of the older adult.
3. A face-to-face approach should strongly be considered as cold calls can put patients off and prevent them from engaging in further conversation.
4. Patients' doctors can play a critical role in recruitment and should introduce the option of research to patients even if they are not directly involved in recruitment.
5. Inconvenience to the older adults should be minimal and offering home visits may be essential to alleviating this. For instance:
 - Transportation should be provided, or home visits should be arranged.

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- Flexibility about appointment times and locations is likely to facilitate greater retention.
 - Given that a good proportion of older adults have caring responsibilities, home visits are therefore invaluable.
6. Older adults are agreeable to research participation but will often seek permission from families. These groups should be targeted about raising their awareness of how research participation can benefit the older population and that their participation is appropriate and necessary. Also, they should be made aware of their own attitudes toward older adults being participants and how this can affect the recommendations they make to them. This can be achieved by families being present when older adults are approached for recruitment.

This chapter has shown that older adults are generally willing and able to take part in clinical research. The insights of the study overall are to be used as a base on which to build future research and to guide the recruitment of older adults in future studies. There is also scope for improving the recruitment and participation process to ensure that all involved are fully aware of the issues that surround the older generation being a part of research and how this can affect the generalisability of the study results. Also, these insights can be used as a base on which to build future research protocols to allow more significant inclusion for those of an older generation who would wish to be involved and thus improve the generalisability of research.

The next chapter seeks to understand the threats to generalisability that occur at the reporting phase of a study. The chapter describes a systematic review that looks at reporting of cohort studies before and after the introduction of the STROBE statement.

CHAPTER 5. ASSESSING THE DESIGN AND QUALITY OF REPORTING OF CKD COHORT STUDIES ASSESSING MORTALITY IN THE ELDERLY BEFORE AND AFTER THE PUBLICATION OF STROBE: A SYSTEMATIC REVIEW.

The previous chapter discussed the perspectives of older, frailer patients on participation/non-participation in an observational cohort study, the European Quality Study (EQUAL) and the impact that non-participation can have not only on a study's internal validity but also its external validity (generalisability). This chapter is dedicated to the third study of the PhD which aims to review the impact of the STROBE statement upon reporting and study design of CKD cohort studies. Inadequate reporting is associated with potentially biased estimates of treatment effects and limits the assessment of a study's strengths, weaknesses and generalisability.

5.1. Introduction

When assessing the value of a study two aspects need considering: the quality of methodological design and the reporting quality.

5.1.1. Study design

The scientific value and reliability of the conclusions drawn from a study are determined to a significant extent by the quality of the study design.

(389)

5.1.1.1. Importance of assessing study design

Before including a study in systematic reviews and meta-analysis, it is essential to assess its methodological design. The quality

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assessment can be utilised in many ways such as the inclusion of studies meta-analysis, guide a sensitivity analysis or meta-regression, weighting studies, or highlighting areas of methodological quality poorly addressed by the included studies. (390) Low-quality studies can lead to a distortion of the summary effect estimate.

5.1.1.2. Assessment of study design

The quality of any study's design can be assessed by considering various methodological aspects and a few tools have been developed for this purpose which includes quality scales, simple checklists, or checklists with a summary judgment for assessment of the risk of bias (391-394). Eighty-six tools for assessing the quality of nonrandomized studies were identified by Sanderson et al. in their systematic review, (393) such as the Oxford quality scoring system (JADAD) (395), the Centre for Reviews and Dissemination-York (CRD) (396) and the Physiotherapy Evidence Database scale (PeDRO) (397) tools for assessment of bias in RCTs. Similarly, the CRD(396), the Scottish Intercollegiate Guidelines Network (SIGN) (398), the Critical Appraisal Skills Programme (CASP) (399) and the Newcastle-Ottawa Scale (NOS) (400, 401) have been developed to assess bias in observational studies.

5.1.2. Study reporting

Good reporting is the final and integral part of the research study and should not be regarded as something new and extra.

5.1.2.1. Study reporting: What is it?

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Good reporting not only informs future research but also contributes to systematic reviews and clinical practice guidelines which in turn inform health policies and clinical practice.

Poor study reporting can be categorised as follows: (389)

- a. Non-reporting of a study, due to failure to publish completed research even if presented at a conference;
- b. Incomplete reporting, which occurs when there is missing of crucial information such as the omission of vital aspects of study's methods (participant selection, interventions, randomisation in trials), incomplete results (data cannot be included in the meta-analysis) or inadequate reporting of harms;
- c. Selective reporting, which occurs when there is biased reporting of data within a published article with emphasis on alternate or sub-group analysis rather than a presentation of main outcomes of the research;
- d. Misleading reporting, which is a result of presenting the study in a more positive way, or with a post hoc change of focus, resulting in a misrepresentation of study findings. For example, in a review of breast cancer trials by Vera-Badillo et al. the authors comment that "...spin was frequently used to influence, positively, the interpretation of negative trials, by emphasising the apparent benefit of a secondary endpoint. The authors found bias in reporting efficacy and toxicity in 32.9% and 67.1% of trials, respectively, with spin and bias used to suggest efficacy in 59% of the trials that had no significant difference in their primary endpoint."(402)

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Inadequate reporting of research is common with several published reviews showing that crucial elements of trial methods and results are commonly missing from journal articles. Poor reporting of trial methods can hamper bias assessment. (403) Poor reporting of interventions can also impede the replication of the study. (404) Poor reporting of data could weaken the determination of effect size. (405, 406) The problems related to poor reporting are common in publically and commercially-sponsored research. (407-409) These deficiencies in reporting have severe implications for clinical practice, future research, development of systematic reviews and clinical practice guidelines, policy-making and ultimately for patients.

5.1.2.2. Importance of study reporting

Accurate and rigorous reporting of research is of utmost importance as published research (peer-review publication) is often the only lasting record of a research study. (410) Mainland in his textbook comments that “incompleteness of evidence is not merely a failure to satisfy a few highly critical readers. (411) It infrequently makes the data that are presented of little or no value.”(412) While some readers might be satisfied with skimming an article or a summary, others will need to critically appraise it in detail to include in a systematic review/metanalysis or to be included in the drafting of clinical practice guidelines. Clinicians, researchers, systematic reviewers and policymakers need a clear understanding of precisely what was done and what was found. Good reporting should be transparent and accurate, should not mislead, should allow replication and be sufficient for

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inclusion in a systematic review or meta-analysis. (413) Inadequate reporting leads to potentially biased estimates of treatment effects and limits the assessment of a study's strengths, weaknesses and generalisability. (414)

5.1.2.3. Study reporting and generalisability

Korn and Ehringhaus et al. in their article make a statement referring to the importance of reporting and implications this has upon the interpretation of a study's generalisability: "clinical research involving human participants can only be justified ethically when such experiments are done to produce generalisable knowledge."(415) Studies should be reported in a way that allows the reader to evaluate the generalisability of the findings to other populations. If the information is not present in the publication the reader of the article is left to decipher how much of the results apply to a particular patient being treated with the disease in question in a different context. Generalisability in an article can be assessed using seven key determinants that provide a more systematic evaluation of this concept : (i) population definition, (ii) definition of outcome, (iii) recruitment of subjects, (iv) inclusion and exclusion criteria, (v) data collection, (vi) subject retention, and (vii) length of follow-up.(416)

5.1.2.4. Assessment of study reporting

Authors and journals have a responsibility to ensure that research is adequately reported. There are several tools that assess the quality of reporting of clinical studies. Reporting guidelines lay down a set of items needed for a clear and transparent reporting of what was done and what

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was found in a research study, thinking about specific issues that could introduce bias into the research. (417) The guidelines are structured advice, often presented as a checklist. The reporting guidelines are based on evidence and are drafted with the consensus of relevant stakeholders such as statisticians, epidemiologists, methodologists, content experts, journal editors, and consumer representatives (multidisciplinary group).

The Consolidated Standards of Reporting Trials (CONSORT) Statement was first introduced in 1996 and revised five years later in 2001(418).

Many medical journals encouraged this scheme, which has helped to improve the quality of reports of randomised trials. Similar initiatives to improve the reporting of other types of research arose after the introduction of CONSORT. (419). The STrengthening the Reporting of OBServational Studies in Epidemiology (STROBE) initiative developed recommendations on what should be incorporated in a precise and thorough report of an observational study. The STROBE statement and checklist were published in October 2007(420, 421). The other reporting guidelines for the main study types include:

- a. Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) for transparent reporting of systematic reviews (422, 423)
- b. CAse REport guidelines (CARE) to improve the completeness and transparency of published case reports (424)
- c. The Standards for Reporting Qualitative Research (SRQR) to improve the transparency of all aspects of qualitative research (425)

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- d. Standards for the Reporting of Diagnostic Accuracy Studies (STARD) to improve the quality of reporting of diagnostic accuracy studies(426, 427)
- e. Strengthening the Reporting of Genetic Association studies (STREGA) which builds on the STROBE statement providing additions to 12 of the 22 items on the STROBE checklist to improve reporting of results of genetic studies(428)
- f. Standards for Quality Improvement Reporting Excellence (SQUIRE) for reporting of quality improvement work(429, 430)
- g. Consolidated Health Economic Evaluation Reporting Standards (CHEERS) for reporting guidance on studies of economic evaluation(431) amongst others(419).

It was envisioned that if these reporting guidelines were adopted by authors and journals, issues such as confounding, bias, and generalisability could become more obvious. Reporting guidelines could also potentially reduce the over-zealous reporting of the research findings, and potentially have an impact on improving the methodology of studies in the long term. (432) Also over time, it was hoped that reporting guidelines would have an impact on improving the methodology of studies by increasing awareness of these issues amongst researchers designing new studies (433, 434).

5.1.3. Impact of guidelines on study design and reporting quality

A review by Samaan Z et al. evaluated adherence to several reporting guidelines in different fields of research. (435) Several studies have assessed the impact of the CONSORT statement on the quality of

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reporting of RCTs (436-439). A systematic review carried out by Pint et al. showed that journal adoption of CONSORT was associated with improved reporting of RCTs (436). A Cochrane review published in 2012 suggested that despite correlative improvements in reporting when CONSORT was endorsed by journals, the completeness of reporting of RCTs remained substandard as journals were not sufficiently explicit to the potential authors regarding their advocacy of the CONSORT statement (439). Moher et al studied the impact of CONSORT on the quality of study design of RCTs reported in four leading medical journals: The British Medical Journal (BMJ), The Journal of the American Medical Association (JAMA), The Lancet (journals that adopted CONSORT) and New England Journal of Medicine (NEJM) (journal that did not adopt CONSORT and was therefore used as a comparator). There was an improvement in reporting, and in the trial design assessed by JADAD scale in all four journals, however, this increase was only statistically significant in the adopter journals (437).

There have been only a couple of studies assessing the impact of the 2007 STROBE statement on the quality of reporting of observational studies. (440, 441) A study by Bastuji-Garin et al. looked at the impact of STROBE on observational studies published in the four dermatology journals with the highest impact factors. The authors commented that reporting was insufficient in a substantial amount of articles published from 2004 to 2010, with the lowest reporting rates for “sample size estimation”, “description of statistical methods” and of “efforts to limit potential sources of bias”, “discussion of external validity”, and

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“discussion of limitations”. The study concluded that the publication of the STROBE statement had failed to significantly influence the quality of observational study reporting and felt this was probably due to the selected dermatology journals not endorsing STROBE. The authors hypothesised that this was probably in keeping with most other medical journals and overall low penetration of STROBE in the period analysed(441).

The impact of the STROBE statement on the quality of reporting and the methodological quality has not been examined in the renal literature. Further, as only two of the 48 nephrology journals (Arab Journal of Nephrology and Transplantation and American Journal of Kidney Diseases) have endorsed STROBE, it cannot be assumed that the introduction of STROBE would have improved reporting of renal studies.

5.1.4. Objectives

Based on the above background and the primary aim of the Doctorate of Philosophy (PhD) the objectives of this review were:

1. To determine whether the publication of the STROBE statement is associated with an improvement in the reporting quality of cohort studies assessing mortality in elderly patients with Chronic Kidney Disease (CKD)
2. To determine whether the publication of the STROBE statement is associated with an improvement in the methodological quality (decrease in risk of bias) of cohort studies assessing mortality in elderly patients with CKD.

5.2. Materials and Methods

5.2.1 Data selection

(a) A systematic literature search was performed in Medline and Embase using the OvidSP interface to identify all papers describing pre-dialysis CKD cohort studies in the elderly (> 65 years) where mortality was reported as an outcome. The search query is presented in Appendix 5.1. Papers published between 1st January 2002 and 31st December 2013 were included, as the KDOQI Clinical Practice Guidelines for Chronic Kidney Disease: Evaluation, Classification, and Stratification were published in 2002 (442). Only articles published in English were considered for the review. The initial search strategy yielded more than 10,000 hits. Hence the number of studies were reduced by restricting the search to European and North American studies. Each article was double sifted at the title, abstract and full-text stage using predefined study inclusion and exclusion criteria by Dr Rao (100%) and a third each by Dr Bruek, Dr Methven and Dr Caskey. Any disagreements about inclusion were resolved by discussion.

The systematic review aimed to cover reporting and design of observational studies before and after the publication of the STROBE statement which was published in October 2007. Reporting and methodological quality were assessed during two time periods: before STROBE between 1/1/2002-31/12/2007 and after STROBE 1/10/2008-31/12/2013, allowing a one-year run-in period after STROBE publication (October 2007). By excluding publications in the immediate twelve months post-STROBE, a period of one year was allowed for submission,

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revision and publication of research adhering to the new guidelines. The analysis was also carried out by dividing the after STROBE period into immediate post-STROBE (1/10/2008-31/12/2010) and late post-STROBE (1/1/11-31/12/13).

5.2.2 Data extraction

The reporting of the selected studies was assessed using the STROBE checklist itself, and the methodological quality assessed using three tools (below). Thirteen of the 22 STROBE checklist items were assessed with two to six questions per item generating 55 questions. The STROBE checklist is presented in Appendix 5.2. These could be answered as “yes,” “partly,” “no,” “unclear,” or “not applicable”. A similar methodology was used to that reported in the publication by Langan et al. (443).

To assess methodological quality, the articles were scored on the Newcastle Ottawa Scale (NOS). At the time this study was designed NOS was recommended by Cochrane for evaluating the risk of bias in observational studies for inclusion in systematic reviews (Appendix 5.3) (400, 401). The articles were also scored using the Scottish Intercollegiate Guidelines Network (SIGN) checklist for cohort studies(398) (Appendix 5.4), and Critical Appraisal Skills Programme (CASP) cohort studies checklist(399) (Appendix 5.5) to estimate the concurrent validity of NOS tool. These three checklists were chosen because they were simple checklists without an additional summary judgement (444).

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The eligible papers that were identified by the sifting process were each scored using the STROBE, NOS, SIGN and CASP checklists by two reviewers (Dr Rao (100%) and a third each by Dr Bruek, Dr Methven and Dr Caskey). Where there was disagreement between reviewers, the consensus was reached by discussion.

5.2.3 Outcome measure

The quality of study reporting was calculated by specific STROBE items and at a manuscript level. A STROBE question score (SQS) was calculated; the number of publications in a period that adequately reported a question divided by the number of publications in which this question was applicable, expressed as a percentage (item analysis). A Manuscript STROBE score (MSS) was calculated for every manuscript; the number of questions (maximum of 55 questions) adequately reported in the publication divided by the number of applicable questions, expressed as a percentage (manuscript analysis).

Similarly, to assess the quality of study design the manuscript NOS score (MNOS), manuscript SIGN score (MSiS) and manuscript CASP score (MCAS) were calculated; the number of questions adequately addressed (in each appraisal tool) divided by the number of applicable items, expressed as a percentage in order to facilitate comparison.

5.2.4 Data analysis

Comparison between pre- and post-period SQS was performed by calculating the risk (proportion) difference between the two groups using the Wald test and respective 95% confidence intervals, with Benjamini

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and Hochberg adjusted p values (False Discovery Rate) to control for multiple testing(445).

MSS, MNOS, MSiS and MCAS were reported as a median with respective interquartile range (IQR). Pre- and post-period median MSS, MNOS, MSiS and MCAS were compared using the Mann-Whitney (MW) test. Despite excluding articles published for one year after the introduction of STROBE, this could potentially have been insufficient for uptake and penetration of the latest information. Therefore a spline linear regression model was used to determine the impact of STROBE over time(446).

Sub-group analyses of MSS were carried out restricting articles to those published in nephrology journals, STROBE endorsing and non-endorsing journals and by journal impact factor in the year that the article was published. Sensitivity analyses were carried out by excluding the outlying MSS if any data points were less than 1.5 interquartile ranges (IQRs) below the first quartile or above the third quartile ($< Q1 - 1.5 \times IQR$ or $> Q3 + 1.5 \times IQR$).

Simple and weighted kappa statistics were used to compare agreement between reviewers for the NOS, SIGN and CASP checklists.

These were assessed at three levels: raters agreement on applicability, clarity (cannot say) and yes/no.

All tests were two-tailed, and p values, < 0.05 were considered statistically significant. Data were analysed using STATA v13.1 (College Station, TX, USA) and SAS v9.3 (SAS Institute, Cary, NC, USA) software.

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5.2.5 Reporting

The study was reported per the PRISMA reporting guidelines. (447)

5.3 Results

5.3.1 Reporting Quality

Figure 5.1 shows the flow diagram of exclusions. Of the 3621 articles initially identified by the Medline and Embase search, 3584 (98.9%) were excluded after the sifting process (Figure 5.1). Only 37 articles met the pre-defined selection criteria for the scoring stage of the review during the inclusion period. Of these 37 articles, 11 were in the pre-STROBE era (1/1/2002-31/12/2007) & 26 in the post-STROBE period (1/10/2008-31/12/2013). Twenty-two of these articles were published in nephrology and 15 in other medical journals. The list of articles considered at the scoring stage of the study is provided in Appendix 5.6.

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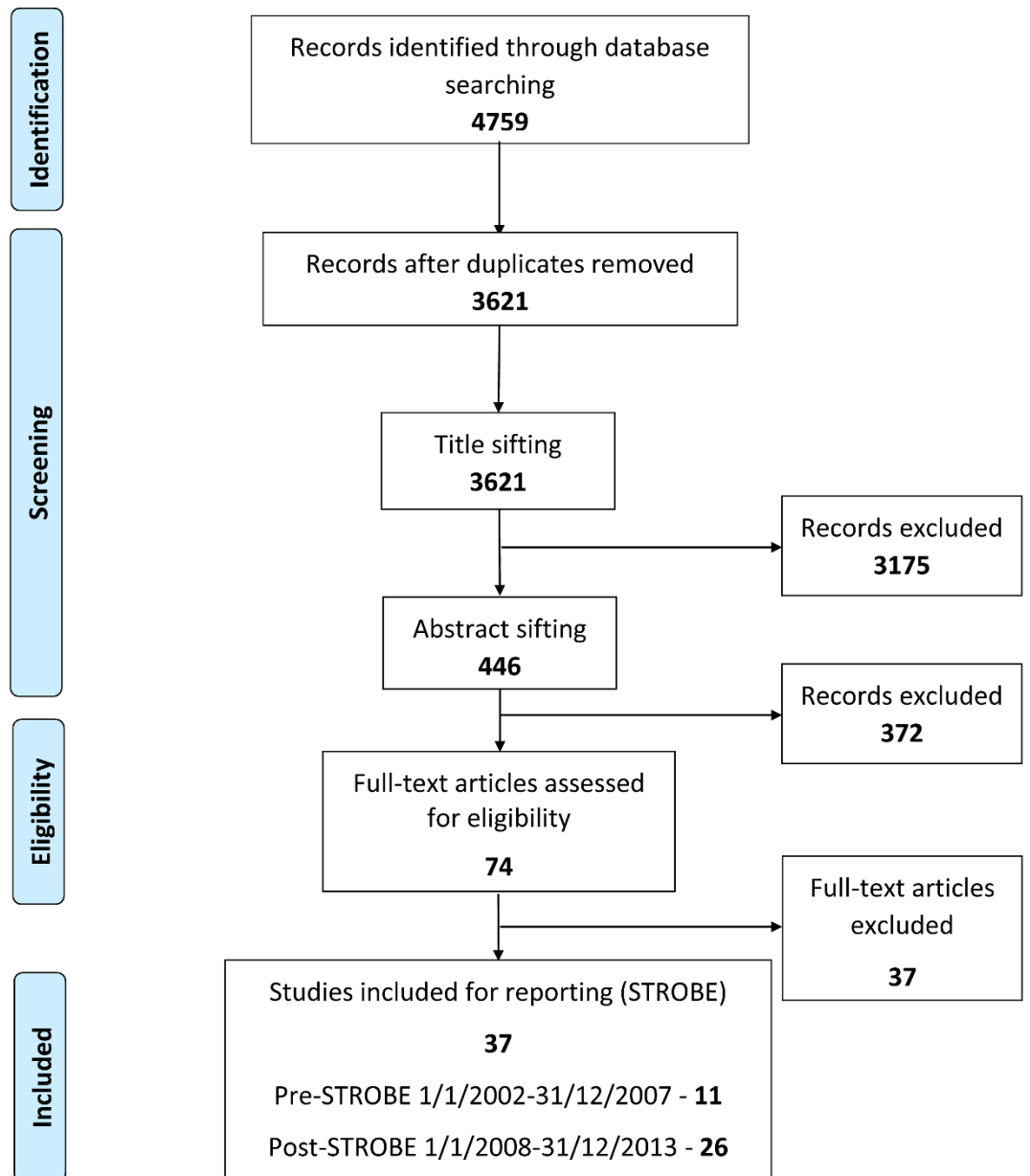


Figure 5.1: Prisma flow diagram

Table 5.1 summarises the STROBE, NOS, SIGN and CASP scores for each of the articles in the pre and post-STROBE period. In most cases,

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reporting quality (STROBE) and methodological quality (NOS, SIGN and CASP) correlated well. However, in some articles, methodological quality scored highly with a low score for reporting and vice versa.

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Table 5.1: Summary of pre and post-STROBE period Manuscript STROBE score (MSS), Manuscript NOS score (MNOS), Manuscript SIGN score (MSiS) & Manuscript CASP score (MCAS) by the article. The citations for the manuscripts are listed in Appendix 5.1

Publication date	Journal	Study Reporting	Study Design		
		MSS	MNOS	MSiS	MCAS
Pre-STROBE					
Dec-02	Journal of American College of Cardiology	76.5	55.6	22.2	33.3
Jun-03	American Journal of Kidney Diseases	77.8	88.9	91.7	100.0
Oct-04	Journal of the American Society of Nephrology	66.7	66.7	50.0	33.3
Apr-05	The Journal of the American Medical Association	88.7	88.9	100.0	100.0
Sep-05	Journal of the American Society of Nephrology	64.7	88.9	80.0	83.3
Dec-05	Journal of the American Society of Nephrology	84.6	66.7	61.5	83.3
Nov-06	British Medical Journal	82.0	100.0	100.0	91.7
Jul-07	Renal Failure	49.1	100.0	88.9	100.0
Jul-07	Journal of the American Society of Nephrology	80.4	100.0	100.0	100.0
Nov-07	Nephrology Dialysis Transplantation	51.1	100.0	80.0	91.7
Dec-07	Archives of Internal Medicine	77.8	88.9	83.3	91.7
Post-STROBE					
Nov-08	Nephrology Dialysis Transplantation	83.0	88.9	83.3	100.0
Dec-08	Nephrology Dialysis Transplantation	84.9	77.8	90.0	83.3
Feb-09	Journal of the American Society of Nephrology	72.9	100.0	83.3	91.7
Apr-09	American Journal of Kidney Diseases	90.0	100.0	69.2	100.0
Jul-09	American Journal of Kidney Diseases	83.7	100.0	100.0	91.7
Jul-09	Clinical Journal of the American Society of Nephrology	75.0	37.5	25.0	33.3
Dec-09	Journal of American Geriatric Society	78.4	100.0	87.5	100.0
Jul-10	Nephrology Dialysis Transplantation	77.6	100.0	90.9	91.7
Oct-10	Journal of Nephrology	39.6	100.0	100.0	100.0
Sep-10	Journal of General Internal Medicine	83.0	77.8	54.5	41.7
Nov-10	Rejuvenation Research	73.6	88.9	80.0	91.7
Sep-11	Clinical Journal of the American Society of	92.2	66.7	90.9	75.0

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	Nephrology				
Jan-12	Nefrologia	50.0	77.8	90.9	91.7
Feb-12	Age and Ageing	83.0	100.0	91.7	100.0
Apr-12	Nephrology Dialysis Transplantation	87.8	88.9	91.7	100.0
Apr-12	The American Journal of Medicine	79.6	100.0	83.3	83.3
May-12	Journal of American Geriatric Society	83.0	88.9	91.7	100.0
May-12	Nephrology Dialysis Transplantation	88.0	100.0	66.7	75.0
Jun-12	The Journal of the American Medical Association	84.9	88.9	66.7	66.7
Jun-12	Clinical Journal of the American Society of Nephrology	83.0	88.9	76.9	83.3
Jul-12	Journal of American Geriatric Society	79.6	88.9	100.0	91.7
Dec-12	Family Practice	84.6	77.8	63.6	83.3
Feb-13	American Journal of medicine	83.0	88.9	75.0	100.0
Apr-13	BMC Nephrology	84.6	100.0	70.0	100.0
May-13	BMC Nephrology	83.0	100.0	88.9	83.3
Sep-13	Clinical Journal of the American Society of Nephrology	90.2	100.0	80.0	66.7

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Details regarding the reporting of the 55 STROBE items in the 37 included cohort studies are shown in Table 5.2. Some of the STROBE question scores showed a ceiling effect as they were already at a maximum level in the pre-STROBE period and could therefore only remain static or decline. Others saw improvements over the period such as “choice of quantitative groups” (30% vs 71%, $p=0.02$), “addressing of losses to follow up” (0% vs 36%, $p < 0.001$), “description of and carrying out sensitivity analysis” (18% vs 58%, $p = 0.01$ & 18% vs 65%, $p = 0.002$) and “usage of flow diagram” (0% vs 19%, $p = 0.01$). However, after adjusting for multiple testing, the change in only two items’ scores remained unlikely to be due to chance; “addressing of losses to follow up” ($p =0.02$) and “carrying out sensitivity analysis” ($p = 0.04$). The majority of STROBE questions showed little improvement between the two periods. Some critical questions, such as hypothesis specification and those important to the interpretation of study validity such as sample size estimation, addressing missing data, addressing loss to follow up, the reason for non-participation and usage of flow diagram continue to be under-reported with less than 50% reporting these items in both periods

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Table 5.2: Median STROBE QUESTION SCORE (SQS), Difference (95% CI) with a p-value of the 55 data items (22 items were further sub-divided to 55 questions in total) in 37 CKD cohort studies, by publication period

Item number	Data Items	Pre-STROBE SQS 1/1/2002-31/12/2007	Post-STROBE SQS 1/10/2008-31/12/2013	Difference	LCI	UCI	p-value	FDR	FDR*
Title and Abstract									
1A	Is the design described adequately in the title or abstract?	0.73	0.69	-0.04	-0.35	0.28	0.83	0.91	0.93
1B	Does the abstract provide an informative summary of what was done and found?	1.00	1.00	0.00	-	-	-	-	-
Introduction									
2	Is the scientific background and rationale for the investigation reported?	1.00	1.00	0.00	-	-	-	-	-
3A	Are any pre-specified hypotheses reported?	0.18	0.23	0.05	-0.23	0.33	0.73	0.91	0.93
3B	Are the objectives reported?	0.73	0.96	0.23	-0.04	0.51	0.09	0.62	0.64
Methods									
4	Are the key elements (ie, retrospective/prospective, cohort/cross-sectional) of the study design presented early in the paper?	1.00	0.92	-0.08	-0.18	0.03	0.14	0.62	.
5A	Are the settings reported?	0.91	1.00	0.09	-0.08	0.26	0.29	0.62	0.74
5B	Are the locations reported?	1.00	0.88	-0.12	-0.24	0.01	0.07	0.52	.
5C	Are relevant dates including periods of recruitment reported?	1.00	0.96	-0.04	-0.11	0.04	0.31	0.62	.
5D	Are relevant dates including periods of exposure reported?	1.00	0.93	-0.07	-0.21	0.06	0.30	0.62	.
5E	Are relevant dates including periods of follow-up reported?	0.91	0.96	0.05	-0.13	0.24	0.58	0.81	0.87
5F	Are relevant dates including periods of data collection reported?	0.73	0.92	0.20	-0.09	0.48	0.17	0.62	0.74
6A	Are the eligibility criteria for participants described?	1.00	0.92	-0.08	-0.18	0.03	0.14	0.62	.
6B	Are the sources of participants described?	1.00	0.92	-0.08	-0.18	0.03	0.14	0.62	.
6C	Are the methods of selection described?	1.00	0.96	-0.04	-0.11	0.04	0.31	0.62	.
6D	Are the methods of follow-up described?	0.91	0.96	0.05	-0.13	0.24	0.579	0.81	0.87
6E	If it is a matched study, are the matching criteria and the numbers of exposed and unexposed described?	0.00	1.00	1.00	-	-	-	-	-
7A	Are all outcomes described if applicable?	0.91	0.96	0.05	-0.13	0.24	0.58	0.81	0.87
7B	Are all exposures described if applicable?	1.00	1.00	0.00	-	-	-	-	-
7C	Are all predictors described if applicable?	0.91	1.00	0.09	-0.08	0.26	0.29	0.62	0.74
7D	Are potential confounders described?	0.91	0.92	0.01	-0.18	0.21	0.89	0.93	0.94
7E	Are all effect modifiers described?	0.73	0.80	0.07	-0.23	0.38	0.64	0.86	0.91
7F	Are diagnostic criteria described if applicable?	0.80	0.92	0.12	-0.15	0.39	0.40	0.73	0.84
8A	Are the sources of data and details of methods of measurement given for each variable of interest?	0.91	0.85	-0.06	-0.28	0.16	0.57	0.81	0.87
8B	If there is more than 1 group, are the measurement methods comparable?	0.75	1.00	0.25	-0.17	0.67	0.25	0.62	0.74
9	Was there any effort to address potential sources of bias?	0.91	0.92	0.01	-0.18	0.21	0.89	0.93	0.94

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10	Did they describe how the study size was determined?	0.00	0.04	0.04	-0.04	0.13	0.31	0.62	0.74
11A	Did they describe how quantitative variables were handled in the analysis?	0.80	0.80	0.00	-0.29	0.29	1	1	1
11B	Did they describe which groupings were chosen for quantitative variables?	0.90	0.83	-0.07	-0.31	0.17	0.58	0.81	0.87
11C	Did they describe why quantitative groups were chosen?	0.30	0.71	0.41	0.07	0.75	0.02	0.17	0.14
12A	Did they describe all statistical methods including those to deal with confounding?	0.91	1.00	0.09	-0.08	0.26	0.29	0.62	0.74
12B	Did they describe methods to examine subgroups and interactions?	0.73	0.72	-0.01	-0.32	0.31	0.96	0.98	0.99
12C	Did they explain how missing data were addressed?	0.27	0.38	0.11	-0.21	0.43	0.50	0.81	0.87
12D	Did they explain if applicable how losses to follow-up were addressed?	0.00	0.36	0.36	0.16	0.56	<0.001	0.02	0.02
12E	Did they describe any sensitivity analysis?	0.18	0.58	0.40	0.10	0.69	0.01	0.14	0.12
Results									
13A	Did they report the numbers of individuals at each stage of the study numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, and completed follow-up and were analysed?	0.64	0.81	0.17	-0.15	0.49	0.30	0.62	0.74
13B	Did they give reasons for nonparticipation at each stage? ^a	0.30	0.48	0.18	-0.18	0.53	0.33	0.64	0.75
13C	Did they use a flow diagram if appropriate?	0.00	0.19	0.19	0.04	0.34	0.01	0.15	0.13
14A	Did they give the characteristics of study participants (e.g., demographic, clinical, and social) and information on exposures and potential confounders?	1.00	1.00	0.00	-	-	-	-	-
14B	Did they indicate the number of participants with missing data for each variable of interest?	0.27	0.15	-0.12	-0.42	0.18	0.43	0.74	0.85
14C	Did they summarize follow-up time (average and total amount)?	0.91	1.00	0.09	-0.08	0.26	0.29	0.62	0.74
15A	Did they report numbers of outcome measures over time?	1.00	1.00	0.00	-	-	-	-	-
15B	Did they report summary measures over time?	0.82	0.92	0.10	-0.15	0.35	0.41	0.73	0.84
16A	Did they give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval)?	0.82	0.92	0.03	-0.24	0.29	0.84	0.91	0.93
16B	Did they detail which confounders were adjusted for and why they were included?	0.90	0.92	0.02	-0.19	0.24	0.83	0.91	0.93
16C	Did they report category boundaries when continuous variables were categorized?	0.90	0.88	-0.03	-0.25	0.20	0.83	0.91	0.93
16D	Did they, if relevant, consider translating estimates of relative risk into absolute risk for a meaningful period?	0.33	0.26	-0.07	-0.43	0.28	0.69	0.90	0.93
17A	Did they report on other analyses done, eg, analysis of subgroups or interactions?	0.64	0.85	0.21	-0.11	0.53	0.19	0.62	0.74
17B	Did they do a sensitivity analysis?	0.18	0.65	0.47	0.18	0.76	0.002	0.04	0.03
Discussion									
18	Did they summarize key results with reference to study objectives?	0.82	1.00	0.18	-0.05	0.41	0.12	0.62	0.70

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19	Did they discuss the limitations of the study taking into account potential sources of bias or imprecision (including discussion of the magnitude of any potential sources of bias)?	0.91	1.00	0.09	-0.08	0.26	0.29	0.62	0.74
20	Did they give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence?	1.00	1.00	0.00	-	-	-	-	-
21	Did they discuss the generalisability (external validity) of the study results?	0.73	0.76	0.04	-0.27	0.35	0.80	0.91	0.93
Other Information									
22A	Did they give the source of the funding in the present study and, if applicable, for the original study on which the present article is based?	0.73	0.77	0.03	-0.28	0.34	0.84	0.91	0.93
22B	Did they give the role of the funders in the present study and, if applicable, for the original study on which the present article is based?	0.36	0.46	0.09	-0.25	0.44	0.60	0.81	0.87

* False Discovery Rate (FDR) calculated excluding questions which had 100% completeness in the pre-STROBE phase.

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Pre- and post-period analyses revealed an increase in MSS (median score 77.8 (IQR, 64.7-82.0) vs 83 (IQR, 78.4-84.9), $p= 0.04$) (see table 5.3). Any pre-STROBE period articles with MSS scores less than 47.4 and post-STROBE period less than 69 were considered to be outliers. Excluding outliers, the improvement in the MSS between the two periods showed a stronger statistical relationship ($p=0.01$). The results were essentially unchanged when restricted to nephrology journals or stratified by STROBE endorsing or non-endorsing journals, though there was less statistical power to test for differences. Journals with impact factor < 5 saw a greater change over the two periods when compared to journals with impact factor ≥ 5 , but given the overlap in the confidence intervals this may have occurred by chance.

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Table 5.3: Summary of quality of reporting as assessed using the Manuscript STROBE Score (MSS)

	Pre-STROBE 1/1/2002-31/12/2007		Post-STROBE 1/10/2008-31/12/2013		p value
	N	median MSS (IQR)	N	median MSS (IQR)	
All Journals	11	77.8 (64.7-82.0)	26	83 (78.4-84.9)	0.04
All Journals (excluding outliers) *	11	77.8 (64.7-82.0)	24	83 (79.6-84.9)	0.01
Nephrology Journals	6	72.3 (64.7-80.4)	16	83.4 (76.3-87.9)	0.09
STROBE endorsing Journals (3)	2	79.9 (77.8-82)	3	90 (83.7-90.9)	0.08
Non-STROBE endorsing Journals (13)	9	76.5 (64.7-80.4)	23	83 (77.6-84.6)	0.10
Impact FACTOR < 5	3	51.1 (49.1-77.8)	16	83 (78-84.6)	0.06
Impact FACTOR ≥ 5	8	79.1 (71.6-83.3)	10	83.4 (79.6-90.0)	0.13

* Excluding articles that were less than 1.5 interquartile ranges (IQRs) below the first quartile (< Q1 - 1.5×IQR). Pre-STROBE=47.4 & Post-STROBE=69

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Time series analysis of MSS showed that there was a significant improvement in the quality of reporting in the latter three years (1/1/11 to 31/12/13) when compared to the first three years (1/10/2008 to 31/12/2010) after the introduction of the STROBE statement (Table 5.4). Longitudinal analysis of the MSS using a spline linear regression model (Figure 5.2), having excluded outliers, suggesting a turning point in 2008 with a slight negative trend in the pre-STROBE period (coefficient - 0.06, SE 0.11) and a positive slope in the post-STROBE period (coefficient 0.21 SE 0.05) but this may have occurred by chance (Slope change coefficient 0.27, SE 0.16; p value=0.10).

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Table 5.4: Quality of the reporting of observational studies as assessed using the Manuscript STROBE score (MSS) over time.

	Pre-STROBE publication (period 1) 1/1/2002 to 31/12/2007	Immediate Post- STROBE publication (period 2) 1/10/2008 to 31/12/2010	Late Post-STROBE Publication (period 3) 1/1/11 to 31/12/13	p value period 1 vs 2	p value period 1 vs 3
N	11	10	14		
Median MSS	77.8	80.7	83.8	0.23	0.003
IQR	64.7-82.0	75-83.7	83-87.8		

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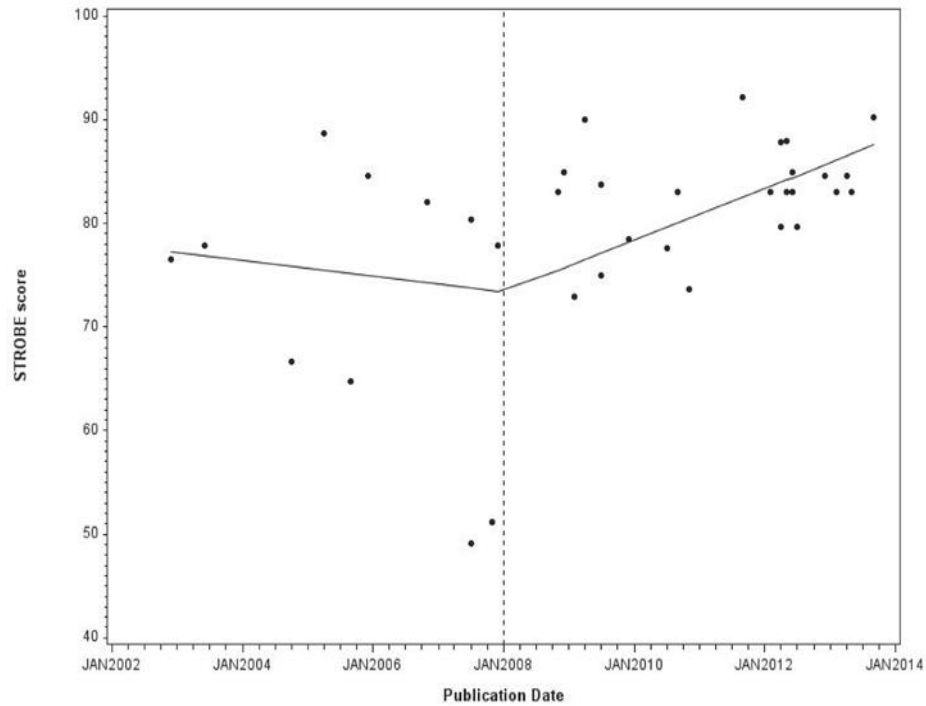


Figure 5.2: Time series of Manuscript STROBE scores (MSS) from spline linear regression models.

5.3.2 Methodological quality (study design)

There was no evidence of any change in the methodological quality of studies in the pre and post-STROBE period using the Newcastle Ottawa Scale (NOS) (median MNOS 88.9% [IQR, 66.7-100] vs 88.9% [IQR, 88.9-100], $p= 0.51$), Scottish Intercollegiate Guidelines Network (SIGN) (median MSiS 83.3% [IQR, 61.5-100] vs 83.3% [IQR, 70-90.9], $p= 0.93$) and Critical Appraisal Skills Programme (CASP) (median MCAS 91.7% [IQR, 83.3-100] vs 91.7% [IQR, 83.3-100], $p= 0.93$) (Figure 5.3).

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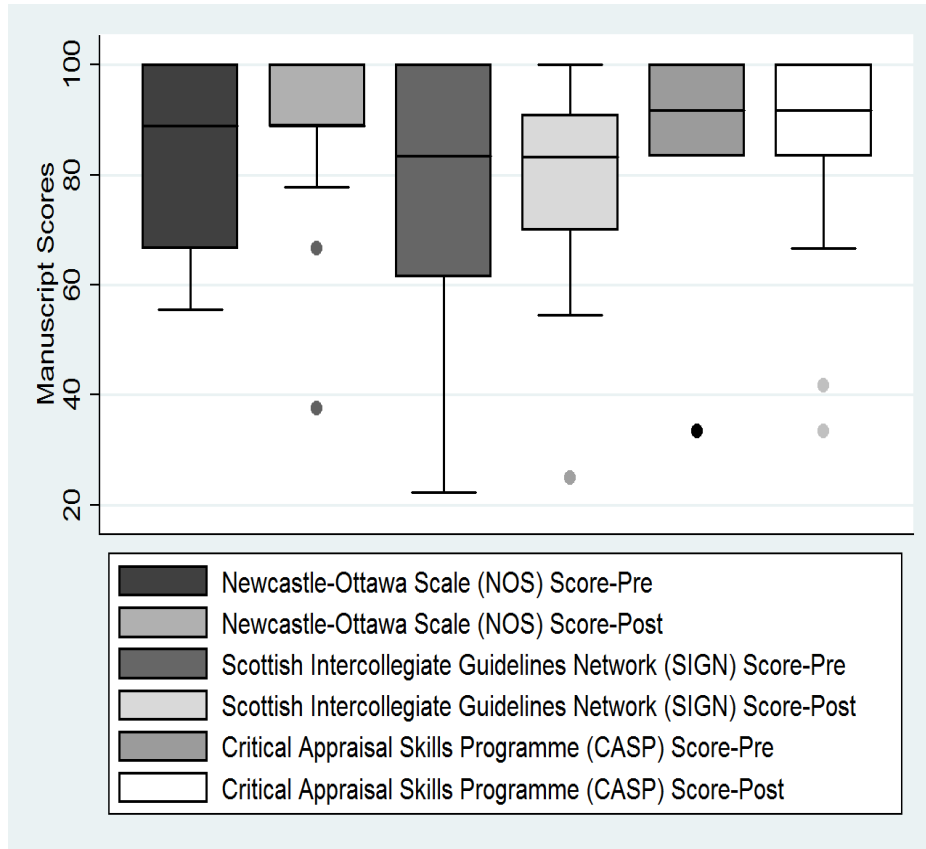


Figure 5.3: Box plot summarising the methodological quality of the studies in the Pre and Post-STROBE period as assessed using the NOS, CASP and SIGN

5.3.3 Inter-rater agreement

The inter-rater agreement for each of the tools was overall inadequate, with the NOS tool having a poor agreement between the three pairs of raters (Table 5.5). The CASP tool fared slightly better compared to the SIGN tool in raters assessment of clarity.

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Table 5.5: Summary of simple and weighted Kappa coefficient, measuring agreement between reviewers for the NOS, SIGN and CASP tool.

	Kappa	Agreement	P value
NOS (weighted)			
Reviewer 1 vs Reviewer 2	0.18	Poor	0.12
Reviewer 1 vs Reviewer 3	0.28	Fair	0.004
Reviewer 1 vs Reviewer 4	0.12	Poor	0.02
SIGN (unweighted)			
Does not apply vs Everything else grouped			
Reviewer 1 vs Reviewer 2	-0.02	poor	0.87
Reviewer 1 vs Reviewer 3	0.05	poor	0.51
Reviewer 1 vs Reviewer 4	0.19	poor	<0.001
Cannot say vs No/Yes grouped			
Reviewer 1 vs Reviewer 2	-0.04	poor	0.62
Reviewer 1 vs Reviewer 3	0.47	moderate	<0.001
Reviewer 1 vs Reviewer 4	-0.04	poor	0.49
No vs Yes			
Reviewer 1 vs Reviewer 2	0.31	Fair	0.004
Reviewer 1 vs Reviewer 3	0.51	Moderate	<0.001
Reviewer 1 vs Reviewer 4	0.24	Fair	<0.001
CASP (unweighted)			
Cannot tell vs No/Yes grouped			
Reviewer 1 vs Reviewer 2	0.90	Very good	0.30
Reviewer 1 vs Reviewer 3	0.72	good	<0.001
Reviewer 1 vs Reviewer 4	0.05	poor	0.05
Yes vs No			
Reviewer 1 vs Reviewer 2	0.69	good	<0.001
Reviewer 1 vs Reviewer 3	-0.06	poor	0.64
Reviewer 1 vs Reviewer 4	-0.07	poor	0.40

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5.4 Discussion

This systematic review assessed the impact of the publication of the STROBE statement on the quality of study design and reporting of methodology. It showed that, after the publication of STROBE, a sizable proportion of the STROBE items and sub-criteria continue to be underreported in CKD cohort studies of mortality in elderly patients. Reporting rates were lowest for hypothesis specification, usage of flow diagrams and addressing missing data. There was evidence of improvement in the reporting quality of CKD cohort studies particularly in the latter three years of the post-STROBE period, which was also seen when looking at the temporal patterns but this may have occurred by chance. There was no evidence that the quality of study design as assessed by three different tools NOS, SIGN and CASP had improved. However, these quality assessment tools have poor to moderate inter-rater reliability and might not be suitable for use without consensus agreement between raters.

5.4.1 The disparity between articles in the two periods

In this review, there were a disproportionate number of articles (2.5 times) in the post-STROBE period compared to the pre-STROBE period. The reason for this disparity could be due to the potential impact of the publication of the CKD guidelines which were published in 2002. (442) This effect has been previously described in the literature. An editorial by Coresh et al. states that “The number of articles in the SCOPUS database retrieved by searching on CKD (June 10, 2012) had increased from 188 in 2000 to 356 in 2002 and 4,035 in 2011”(53)

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5.4.2 Reporting quality

Inadequate reporting not only hinders meticulous assessment by others of the strengths and weaknesses in study design, conduct, and analysis, it affects the judgement of whether and how results can be included in systematic reviews and also impacts on the reader assessment of the studies generalisability (448). The results of this review are consistent with other studies assessing deficiencies in reporting of individual STROBE items such sample size, use of flow diagram and reporting of missing data (440, 441, 443, 449-452).

As previously mentioned several studies, including a Cochrane review, have demonstrated improvements in reporting quality of randomised control trials (RCTs) after the introduction of the Consolidated Standards of Reporting Trials (CONSORT) statement with a significant improvement in journals endorsing this guideline statement(436-439, 453). An RCT has also shown that using reporting guidelines in the peer review process improves the quality of manuscripts (454). Our study showed weak evidence of improvement in the quality of reporting of CKD cohort studies over time following the introduction of the STROBE statement. The improvements, unfortunately, fell short of the intended expectations when compared to the impact the CONSORT statement had achieved upon the reporting quality of RCTs. These results were similar to the only other study looking at the quality of reporting of observational cohort studies, published in the dermatology literature. Those authors attributed the lack of improvement to the short follow up period after STROBE introduction (2008–10)(441). However, in our study, the small

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improvement could be attributable to the fact that the reporting of nephrology literature in the pre-STROBE period was already of a higher standard (median MSS 77.8 IQR 64.7-82.0) in comparison to dermatology literature (median score 58 IQR 46-73).

Journal endorsement of reporting guidelines has also been shown to improve the reporting quality of manuscripts submitted to journals (454). However, given that only two medical journals (British Medical Journal & Ageing) and one renal journal (American Journal of Kidney Diseases) included in this review had endorsed the STROBE statement, any evidence of improvement in reporting quality of cohort studies in nephrology literature is probably owed to the penetration of the STROBE statement over time rather than to its endorsement by journals (455). The lack of improvement of reporting standards seen in the STROBE endorsing journals is not an indictment of these journals but may be attributable to the small sample size to accurately test for differences between the groups. An important observation that was made during the process of this review was that despite studies having similar crude scores, reflected by their similar MSS, some studies had failed to adequately report essential criteria and had significant omissions. This is because a similar weight is attributed to all items on the checklists.

5.4.3 Methodological quality

For most of the articles included in this study reporting and methodological quality were well correlated. However, the assessment of the methodological quality of a study is dependent mainly on adequate reporting of the research. Therefore, drawing any inferences about a

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study's design quality is made harder if the reporting quality is inadequate. One of the primary goals of reporting guidelines was to improve reporting clarity and not necessarily improve the quality of research, but in due course achieve this as an indirect effect. Due to the interchangeable usage of the terminology 'reporting quality' and 'methodological quality', the STROBE statement has often been used inappropriately for the assessment of methodological quality of observational research (434). There are some assessment tools that have been developed to assess quality and risk of bias in observational studies with only half of the identified tools having described their development or validity and reliability (444). The review by Sanderson et al. revealed the lack of an ideal tool for assessing the quality of observational epidemiological studies (444). The bias assessment tools used in this study (NOS, SIGN and CASP) were subjective, differed by content, format and validity. The bias assessment tools identified deficiencies in the articles relating to consideration of participants lost to follow up (attrition bias), exposure level or prognostic factor measured only once (detection bias), and inadequate methods of outcome assessment (detection bias). However, given that the assessment of methodological quality is largely reliant on the reporting of study design, one might, therefore, fail to detect differences in design quality if reporting is inadequate. Also given the latency period of designing a new study, undertaking it and then publishing it, might have been simply too soon for the STROBE statement to have influenced the methodological quality of studies. The NOS tool was previously recommended by Cochrane for

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evaluating the risk of bias, but published literature has demonstrated poor inter-rater reliability between individual reviewers (456, 457). The results of our study are consistent with these findings as all the three tools (NOS, SIGN and CASP) showed poor agreement between individual reviewers. The usability of a tool depends on its clarity. Moreover, the tools contain items whose scoring is subjective and dependent on reviewers' perceptions and domain knowledge. Cochrane now recommends the ACROBAT-NRSI bias assessment tool for non-randomized studies which has been developed by members of the Cochrane Bias Methods Group and the Cochrane Non-Randomised Studies Methods Group (458, 459). However, at the time of drafting this manuscript, this tool remains to be tested for consistency between individual reviewers. This tool has since been replaced by the Risk Of Bias In Non-randomised Studies - of Interventions (ROBINS I) tool. (460)

A strategy to improve inter-rater agreement would be to provide training to reviewers before the implementation of the tools. Due to the poor reliability of the tools demonstrated here, it should be strongly considered that each study should be assessed by at least two reviewers before inclusion in a systematic review/meta-analysis.

5.4.4 Strengths and limitations

One of the strengths of this review is that it assessed the impact of STROBE upon both the quality of reporting and study design. The study also has good internal validity as the selection, and evaluation processes were independently performed by two reviewers. However, as the articles were included from one field of medicine (CKD), we must be

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cautious in generalising our findings to other areas. The other limitation of the study was that it only covered articles from Europe and North America. There was also an imbalance in the number of studies assessed in the two periods probably due to the KDIGO CKD guidelines which were published in 2002. This imbalance could have potentially introduced a lack of power to detect a difference in quality. It was also impossible to blind the reviewers to the publication date during the sifting stage of the review, and the journal name during the review of quality which could have biased the reviewers' assessment of the quality of the study. Finally, while this review examined a five-year period post-STROBE, it is possible that it failed to find any benefit for methodological quality due to the extended latency period between designing a new study, obtaining funding, undertaking data collection, analysis and publication.

5.4.5 Conclusion

This study highlights continuing deficiencies in the reporting of observational studies in the nephrology literature. However, the publication of the STROBE statement may have positively influenced the quality of some aspects of observational study reporting. There was no evidence, however, that methodological quality improved over this time-period. With continued efforts from researchers and with a particular focus on the domains identified as deficient by the STROBE statement and bias reporting tools, this presents an opportunity to improve the validity of observational research in nephrology. With increased awareness by authors and editors regarding compliance of manuscripts to

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the STROBE statement and journal endorsement of the STROBE statement, we hope that not only reporting but also the design of future studies will be improved.

CHAPTER 6 SUMMARY AND CONCLUSIONS

CKD is recognised as a growing and an important public health issue, which affects up to 14% of the population of the developed world. (155-157) CKD is prevalent in the elderly and is associated with increased morbidity and mortality. (158, 159, 383) Both observational studies and RCTs play a valuable role in nephrology and have informed clinical practice. As with clinical trials, the most significant challenge to observational research is external validity. External validity is often used interchangeably with the term "generalisability" (106). Threats to generalisability can occur at the design stage due to selective inclusion criteria, at the recruitment stage due to non-participation of specific groups, and finally at the reporting stage due to poor reporting.

The works presented in this PhD thesis attempts to understand more fully the various factors that could affect a study's generalisability. The study examined was the EQUAL Study, an international prospective observational cohort study to determine when dialysis should be initiated in elderly patients. (129). The PhD was a mixed method study of convergent parallel/ triangulation design with the results of the individual studies being merged/triangulated at the phase of interpretation (Figure 6.1) to answer the overarching question of the thesis “ *What are the factors that affect the generalisability of cohort studies?* ”.

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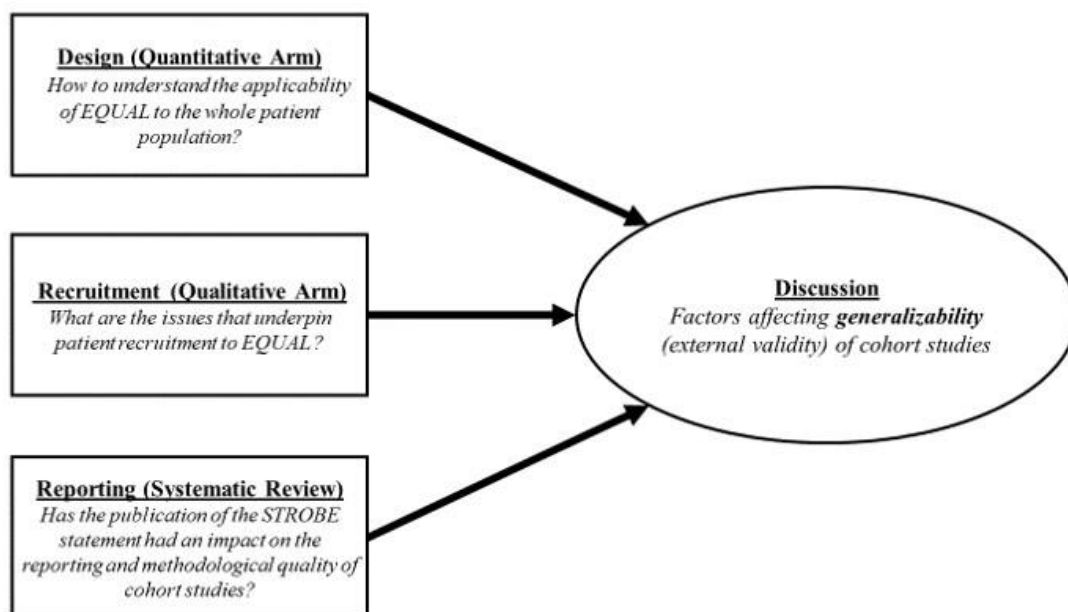


Figure 6.1: Factors affecting the generalisability of EQUAL

6.1. Quantitative arm

How to understand the applicability of observational data to the whole patient population by linking to existing GP databases (Chapter 4)?

A general challenge of all research and particularly that of a cohort study is external validity (generalisability). (107) For the results of any study to be useful, their relevance beyond the studied population needs to be understood, i.e. their generalisability. (107) In the North American Atherosclerosis Risk in Communities (ARIC) study, generalisability was examined by nesting study patients in communities covered by broad surveillance. (97, 98) In the UK, four key GP databases hold longitudinal patient data which have shown to be generalisable to the UK regarding demographics and crude prevalences of significant conditions (180, 183, 461). Although various methods have been used

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in evaluating the generalisability of RCTs, no published studies have used GP databases for understanding the generalisability of either RCTs or that of observational research. (462, 463)

This study showed that patients in EQUAL were more likely to be younger, male and from an urban setting compared to the primary and secondary care cohort patients. The EQUAL patients were also less likely to have cardiovascular, cerebrovascular, peripheral vascular and rheumatic diseases, with no prevalence of dementia. The EQUAL patients were more likely to start RRT, and the probability that they were alive at one year compared to the primary and secondary care patients was greater. The overall better health of EQUAL patients meant that they were less liable to be admitted to hospital for illnesses.

Future Directions

The results of this study suggest that some things might be helpful to improve the generalisability of observational data.

- Future studies (RCTs and observational research) could make a comparison between the study (experimental) and the eligible populations at the same time as the study is conducted.
- If this is not achievable, GP databases and chronic disease registries should be used to understand how the results of the studies (RCTs and observational studies) would be generalisable to the real-world population.
- Statistical techniques such as probabilistic sensitivity analysis (Episens model, Orsini et al.) may help to quantify the effect of bias. (257)
Researchers can use this technique to report results that incorporate their

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uncertainties regarding systematic errors and hence avoid overstating their certainty about the effect under study. (257, 258)

6.2. Qualitative Arm

What are the issues that underpin patient recruitment to the European QUALity Study on treatment in advanced chronic kidney disease - EQUAL (Chapter 3)?

Many research projects fail to recruit their targeted numbers, and it is, therefore, essential to gain an understanding of the reasons why individuals choose to participate or otherwise. (333) To date, there are no published studies that have attempted to study the perceptions regarding research participation of elderly multi-morbid patients using qualitative methods, as in this study. This study is also unique in capturing views expressed by those who had declined to participate in research (the declined group).

The study showed that patients who agreed to participate in research often report being activated in their own healthcare and this seemed to relate to their decision to take part in research. Altruistic morals had a strong influence on participation in the EQUAL study. Interestingly, however, the relationship was complicated as the majority of the participants had also expressed self-interest which suggested that this could be a prerequisite for altruism. The issue of caring responsibility and transportation were the main reasons causing inconvenience and negatively influenced participation. Interpersonal trust between the patient and their physician was a substantial factor influencing participation.

Future Directions

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The results of this study suggest a number of things might be helpful to improve the recruitment of older adults.

- Recruiters could consider adopting different recruitment strategies for various demographic groups. (464)
- An opt-out recruitment method may be considered as a strategy to optimise recruitment in research. (465, 466)
- A face-to-face approach maybe strongly considered as this approach can engage in further conversation with the potential participant.
- It may be beneficial for families to be present when older adults are approached for recruitment. However, not all (older adults, or other) patients would want their families present and unless it is thought that they are not competent to make a decision. Could this be imposed?
- Patients physicians should probably play a critical role in at least introducing the option of research to patients even if they are not directly involved in recruitment.
- Inconvenience to the older adults should be minimal with either transportation provided if the study requires a visit to the hospital, or home visits arranged.
- Finally, flexibility about the appointment times and locations is likely to facilitate participation and also promote retention.

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6.3. Systematic Review

Has the publication of the STROBE statement had an impact on the quality of reporting and the methodological quality of cohort studies in nephrology (Chapter 5)?

Good reporting is crucial as it not only informs future research but also contributes to systematic reviews and clinical practice guidelines. This, in turn, informs health policies and clinical practice. (410, 467, 468) Good reporting also assists the reader in making judgements about the generalisability of the findings to other populations. STROBE guidelines were developed to improve the quality of reporting of observational studies (420, 421). The impact of the STROBE statement on the quality of reporting and the methodological quality has not been examined in the renal literature. Further, this is the first time a study has assessed the impact of the introduction of a reporting guideline on both the design of studies and the quality of the subsequent reporting.

This review showed that that, after the publication of STROBE, a sizable proportion of the STROBE items and sub-criteria continue to be underreported in CKD cohort studies of mortality in elderly patients. There was, however, evidence of improvement in the overall reporting quality of CKD cohort studies particularly in the latter three years of the post-STROBE period. There was no evidence that the quality of the study design had improved in the time frame studied.

Future Directions

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The results of this study suggest that some things might be helpful to improve the reporting of cohort studies.

- Increased awareness by authors and editors regarding the compliance of manuscripts to the STROBE statement could potentially improve journal reporting.
- Journal endorsement of the STROBE statement could have an impact not only on reporting but also the design of future studies. (454)

6.4. *Reflections on the Mixed Method Approach Adopted*

The mixed methods approach of this PhD thesis has aided a breadth and depth of understanding of some of the issues with corroboration of the results from the quantitative and qualitative arms of the study. (469-472) Using a combination of methods allowed me to consider several rather than just one face of the problem giving a richer and a truer account. Reliance on one method can result in bias. For example,

- a. Measurement bias: For example response bias, in which participants sometimes tend to tell you what you want to hear. With a mixed method triangulated approach one can combine self-reported and observational research methods to help balance out the problem.
- b. Sampling bias: Sampling bias, e.g., omission bias occurs when the researcher covers only some parts because it is more convenient (inclusion bias). In this case, the qualitative study was conducted in three of the ten EQUAL recruitment sites, but the sample was representative to corroborate some of the results of the

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quantitative study. Therefore, mixed methods (triangulation) combines the different strengths of these methods to ensure one gets sufficient coverage.

Some of the issues are illustrated below with representative quotes from the qualitative study. In both the quantitative and the qualitative studies there was evidence that older people were more likely to decline participation. The quantitative arm of this study showed that patients in EQUAL were three and ten years younger than patients in the secondary care cohort and primary care cohort respectively. There were decreasing odds of participation; for every 5-year age band increase, the likelihood of participation reduced significantly. The qualitative arm provided insight into some of the reasons behind non-participation of the elderly (≥ 75 years) with issues of convenience such as caring responsibilities, reliance on friends and family and transportation being predominant.

“I: When you were approached to take part in the EQUAL study you did mention that there was too much on at that time, would you mind elaborating?”

R: Well as I said my husband does not endure very good health, he is a diabetic, he is under the urinal clinic, he has had heart surgery, he is having problems even with his sugar levels at the moment, and I have to do a lot for him. I have to help him dress, I help him to wash, and it is all happening now. Up until this year, he was quite independent, so these sorts of things were all going through my mind.”
BRL_DNA_09

“I: Please can we start with your background, and then going on to your kidney condition.

R: Mm. Well as I say I, I cannot go very far because of him, you know, I have got make sure he is ok....He fell down in the greenhouse....And we had to call the ambulance....., we do not go out very much now, we used to, he cannot walk very far. He could not; he cannot walk from there to there without getting out of breath.

R: My daughter, she has just gone back yesterday, uh, she comes down from Sheffield to help, but she cannot afford to come down here all the time because her husband works in Holland and she is got to be at home with her children”
BRL_DNA_14

“R:I cannot really go out if it is peeing with rain, and I am a bit limited, I cannot drive any longer, I have been banned from driving.

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I: Is that to do with your eyesight?

R: I did lose this, my right eye, I have completely lost that, had a haemorrhage and it is got better, but it is not good enough for drivingSo, it does limit you to what you can do, you know, you have to rely on people, and you have to rely on transport to get you to the hospital etc.” OXF_DNA_05

The quantitative arm has shown that higher Charlson Co-morbidity Index (CCI) was associated with lower odds of participation in EQUAL, with patients with $CCI \geq 4$ 30% less likely to participate in EQUAL (comparing apparently eligible patients in secondary care with those recruited to the EQUAL study). The qualitative interviews provided some further explanations for non-participation, with frailty and functional status, which is closely linked to co-morbidity, being raised as a barrier to research participation.

“R: I’ve got to the stage now where even doing vacuuming I can only vacuum for so long, and then I have to have a sit down and have a breath – breather I should say, and ugh certain jobs in the house are now becoming a little bit too difficult to try and do, but obviously, age is – has crept up on me and ugh I try and do what I can when I can. I feel now especially in the afternoon I do need to take a rest it is about an hour sleep, and then I feel I can carry on a little bit more, but having said that – that also times when I have got a job to keep awake” BRL_DNA_09

Related to this, the interviews suggested a link between non-participation and self-reported mobility, something which often accompanies deteriorating health. Finally, the declined group also talked about an increased burden from hospital appointments affecting the decision to participate in the study.

R: It is because, this, this is not to do with my kidneys, this is purely to do with the fact that I cannot balance.....Moreover, I do feel very vulnerable. Moreover, that is frightening....Moreover, the fewer times I have to out of that front door the better it is for me.....I know that it won’t help my case, but research has got to take place to help people in the future, I’m well aware of that, but I’m not just an ordinary kidney patient, I’ve got another problem as well you see, and

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I thought I couldn't set myself up for all this. Because of my balance, I am frightened I will fall. If I fall and break an arm, I am in real serious trouble" BRL_DNA_13

The quantitative arm showed that patients in the primary and secondary care cohort had more than twice the rate of hospital admissions compared to patients in EQUAL. Although this link was not overtly established in the qualitative interviews, the declined group suggested that they had a higher burden of hospital appointments which could be a proxy for increased hospitalisation.

"R: Well what it was, with all the clinics. I mean this is sort of like injections, foot clinic, diabetic clinic, renal clinic and the eye clinic, everybody seems to want blood..... I cannot remember, I was panicking (laughter) it is all sort of more visits and more blood.....It was "help, please, no more" was my reaction." OXF_DNA_17

Therefore, the two arms account for the information obtained, and the qualitative findings provided some insights into the patterns that emerge from the quantitative data, and hence mixed methods are particularly valuable.

6.5. Summary

In summary, this thesis has described the various factors presenting threats to the generalisability of cohort studies occurring at design, recruitment and reporting stages of cohort studies using the example of a cohort study of advanced CKD in the elderly -EQUAL. It has done this through the use of a mixed-methods approach and in doing so has demonstrated the importance of multiple/mixed methods as an approach to understanding complex topics (generalisability of cohort studies), understanding issues in depth and improving reliability and validity of findings. Finally, this thesis provides recommendations and issues to be

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taken into consideration for enhancing generalisability (external validity) of cohort studies going forward.

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Appendices

APPENDICES

Appendix 2.1: EQUAL Patient Invitation Letter

Trust logo

Renal Unit address

Tel:
Fax:

<Patient name>
<Patient address>

<Date>

Dear <Title & surname>,

Re: The European Quality (EQUAL) Study on treatment in advanced chronic kidney disease

I am writing to ask if you would consider taking part in this research study. It aims to establish the treatments that give patients aged 65 years and older with low levels of kidney function the best prognosis and quality of life. The findings will hopefully provide helpful, patient-centred information to patients in the future with advanced kidney disease to help them make decisions about treatment.

Your kidney care will continue as normal, we just want to collect information about the care you receive and how it affects your symptoms and quality of life. To do this, with your consent, a research nurse will contact you to arrange a convenient time and place for your visits. [It may be possible to arrange a home visit if this would suit you.]* They will ask you questions about your health and undertake a short physical examination. They will then ask you to answer some questions about your quality of life, symptoms and satisfaction with treatment. A blood test will be taken. With your consent, information will be gathered from your clinical records by the nurse. The whole visit should take 30-45 minutes. More details can be found on the enclosed pamphlet.

If you are happy for one of the research nurses to contact you with more information about the study then you don't need to do anything – someone will get in touch in the next couple of days. If you would prefer not to be contacted, just let me know by calling the number at the top of this letter.

With best wishes.

Yours sincerely,

<Title & name of local healthcare team member>
<Job title>

Enc: EQUAL: An introduction for patients

** Section in parenthesis may not be included in some sites.*

Appendices

Appendix 2.2: EQUAL Pamphlet “An introduction for patients”

Additional information

For more detailed information regarding this study you can ask your doctor or nurse or contact the EQUAL investigators (contact details below). Alternatively you can find more information about the EQUAL study at www.equal-study.org.

The EQUAL Collaborating Investigators

UK National Coordinating Centre

Dr F Caskey and Mrs H McNally

Richard Bright Renal Unit, Southmead Hospital, Bristol. BS10 5NB

Tel: 0117 323 4300 Email: helen.mcnally@nbt.nhs.uk

European Coordination Centre

ERA-EDTA Registry, Amsterdam

Dr K.J. Jager and Dr M.W.M. van de Luitgaarden

Email: m.w.vandeluitgaarden@amc.uva.nl



A European Quality Study

**on treatment in advanced chronic
kidney disease**

An introduction for patients

The EQUAL Study Pamphlet, version 2.0, 1st November 2013

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Introduction

People are generally living longer nowadays with better treatment of their medical conditions. One consequence of this is that an increasing number of people are finding that they have reduced kidney function and need to attend a specialist kidney clinic. This is particularly true for people over 65 years of age.

Surprisingly little is known about the symptoms older patients get as their kidney function decreases or what treatments lead to the best results in this age group.

What questions will be addressed by this study?

For patients 65 years of age and older with kidney function that has reached 20% for the first time in the last 6 months:

- When should treatment be started for the best results?
- Which signs and symptoms are most important?
- What is the best way to measure kidney function at these levels?
- What is important when deciding if (and when) to start dialysis, bearing in mind other medical conditions and home circumstances.

Why have I been chosen?

You have been chosen because you are aged 65 years or older and your kidney function has reached a level (about 20% of normal) below which some patients begin to have symptoms related to their kidney function.

What will happen if I take part?

If you agree to take part in the study, your doctors and nurses will continue to treat you as normal. Using your medical notes and physical examination information will be collected about you and the treatment you receive for a period of 4 years. Every 3 to 6 months you will be asked to complete a questionnaire on how you feel and whether you are satisfied with your current situation. At up to three points in the study you will be asked for a blood sample that would not normally be required.

Do I have to take part in this study?

No, it is up to you to decide whether or not to take part. If you decide to take part you are still free to withdraw at any time and without giving a reason.

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Appendix 2.3: EQUAL Patient Information Sheet



EQUAL UK Lead Investigator:
EQUAL UK Lead Research
nurse:
www.equal-study.org

Dr Fergus Caskey
Helen McNally

North Bristol 
NHS Trust

Richard Bright Renal Unit
Southmead Hospital
Bristol
BS10 5NB

Tel: 0117 323 4300
Fax: 0117 323 8677

Patient Information Sheet

The EQUAL Study

The European Quality Study on treatment in advanced chronic kidney disease

Invitation

We would like to invite you to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it would involve for you. Please take time to read the following information carefully and discuss it with friends, relatives and your GP if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

Thank you for reading this.

What is the purpose of the study?

The study aims to establish the treatments that give patients aged 65 years and older with low levels of kidney function the best prognosis and quality of life. The findings will hopefully provide helpful, patient-centred information to patients in the future with advanced kidney disease to help them make decisions about treatment.

Why have I been approached?

You have been chosen because you are aged 65 years or older and your kidney function has reached a level (about 20% of normal) below which some patients begin to have symptoms related to their kidney function.

Do I have to take part in this study?

No, it is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. This will not affect the standard of care you receive.

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What will happen to me if I take part?

If you agree to take part in this study your treatment plan and care will not alter.

A research nurse will contact you to arrange a convenient time and place for your initial visit. At this visit, they will ask you questions about your health and undertake a short physical examination. They will then ask you to answer some questions about your quality of life, symptoms and satisfaction with treatment. A blood test will be arranged. With your consent, information will be gathered from your clinical records by the nurse. The whole visit should take 30-45 minutes.

Follow up visits will be arranged with you at a time and place that suits approximately every six months. These do not involve additional blood and urine collections. If your kidney function decreases to 10% or you and your consultant decide you should start dialysis, follow up visits will start taking place every 3 months. A second set of blood tests will be requested around this time.

Up to three blood samples (one at the beginning of the study and up to two later in the study) will be stored anonymously outside the UK for the current study and possibly future research.

What are the possible disadvantages and risks of taking part?

The only disadvantage that may arise from taking part in the study would arise from the additional time spent with the research nurse or from being asked questions about your quality of life and decision making.

Will any genetic tests be done?

A blood sample will be taken at your first study visit for DNA analysis. This will be used to better understand the link between genetic factors and risk of kidney disease. This DNA analysis will not be used to tell us whether kidney disease might affect other members of your family. If you would prefer for this not to happen you may indicate this on the consent form.

What are the possible benefits of taking part?

It is unlikely that the results of this study will directly benefit your care. The information we get from this study may, however, help us to treat future patients with kidney failure better.

What happens when the research study stops?

At the end of the research you care remains the same. We would like to have the opportunity to contact you or your GP in the future to see how you are and what your general health is like. We may also want to contact you or your GP for your opinion about your treatment and how satisfied you have been with your care.

Will my taking part in this study be kept confidential?

All information collected about you during the course of the research will be kept confidential. A unique study identifier will be generated to identify you so that your name and address will never be entered onto the main study database. A "key" linking your study identifier to you will be kept securely in the local centre to allow monitoring of the research and in the national coordinating centre in Bristol to enable linkage with national registries such as the UK Renal Registry. This key will be destroyed 10 years after the end of the study.

What will happen to the results of the research study?

The results of this study will be published in national and international journals. You will not be identified in any reports or publications. You will be able to obtain a copy

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of the published results from the ERA-EDTA website (www.era-edta-reg.org) or writing to:

Dr Fergus Caskey
Department of Renal Medicine
Richard Bright Renal Unit
Southmead Hospital
Bristol
BS10 5NB

Who is organising and funding the research?

The study has been organised by a group of researchers in five European countries (Germany, Italy, The Netherlands, Sweden and The UK), lead by Dr Kitty Jager in Amsterdam. The research is funded by a grant by the European Renal Association – European Dialysis and Transplant Association. The doctors conducting the research are not being paid for including and looking after the patients in the study.

Who has reviewed the study?

In the UK, the study has been reviewed by the National Research Ethics Service (NRES) Committee South West – Central Bristol

Contacts for Further Information

If you do require additional information, please contact:

Dr Fergus Caskey
Richard Bright Renal Unit
Southmead Hospital
Bristol
BS10 5NB
Tel: 0117 323 2312

Complaints

For independent advice you can discuss the study with your consultant nephrologist or contact the North Bristol Advice and Complaints Team:

Advice and Complaints Team,
Frenchay Hospital,
Beckspool Road,
Bristol BS16 1JE
Tel 0117 340 3741 or 3076
<http://www.nbt.nhs.uk/patients-carers/advice-complaints>

Thank you for reading this. We hope you agree to take part in this study

You will be given a copy of the information sheet and a signed consent form to keep

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Appendix 3.1: Codes related to Renal Replacement Therapy in The Health Improvement Network-THIN (read codes) and Hospital Episode Statistics (HES)

Medcode	Description
ZV42000	[v]kidney transplanted
Z94.0	kidney transplant status
T86.1	kidney transplant failure and rejection
N16.5	renal tubulo-interstitial disorders in transplant rejection
TB00100	kidney transplant with complication; without blame
TB00111	renal transplant with complication; without blame
SP08300	kidney transplant failure and rejection
SP08J00	chronic rejection of renal transplant
SP08N00	unexplained episode of renal transplant dysfunction
SP08R00	renal transplant rejection
SP08T00	urological complication of renal transplant
SP08W00	vascular complication of renal transplant
7B00211	allotransplantation of kidney from cadaver
7B00212	cadaveric renal transplant
7B00300	allotransplantation of kidney from cadaver heart-beating
7B00400	allotransplantation kidney from cadaver heart non-beating
7B00600	xenograft renal transplant
7B00y00	other specified transplantation of kidney
7B00z00	transplantation of kidney nos
7B01500	transplant nephrectomy
7B01511	excision of rejected transplanted kidney
7B06300	exploration of renal transplant
7B0F.00	interventions associated with transplantation of kidney
7B0F100	pre-transplantation of kidney work-up; recipient
7B0F300	post-transplantation of kidney examination; recipient
7B0Fy00	os interventions associated with transplantation of kidney
7B0Fz00	interventions associated with transplantation of kidney nos
SP08C00	Accelerated rejection of renal transplant
SP08E00	Acute rejection of renal transplant - grade I
SP08F00	Acute rejection of renal transplant - grade II
SP08G00	Acute rejection of renal transplant - grade III
SP08H00	Acute rejection of renal transplant
SP08J11	Chronic transplant nephropathy
SP08K00	Chronic rejection of renal transplant - grade 1
SP08L00	Chronic rejection of renal transplant - grade II
SP08M00	Chronic rejection of renal transplant - grade III
SP08P00	Stenosis of vein of transplanted kidney
SP08Q00	Aneurysm of artery of transplanted kidney
SP08S00	Aneurysm of vein of transplanted kidney
SP08V00	Very mild acute rejection of renal transplant
SP08X00	Rupture of artery of transplanted kidney
SP08Y00	Rupture of vein of transplanted kidney
SP08Z00	Thrombosis of artery of transplanted kidney

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Z99.2	dependence on renal dialysis
ZV45100	[V]Renal dialysis status
14V2.00	H/O: renal dialysis
14V2.11	H/O: kidney dialysis
4I29.00	Peritoneal dialysis sample
4N...00	Dialysis fluid examination
4N0..00	Dialysis fluid urea level
4N1..00	Dialysis fluid creatinine level
4N2..00	Dialysis fluid glucose level
4N3..00	Peritoneal dialysis fluid cell count
4N4..00	Dialysis fluid potassium level
4N5..00	Dialysis fluid sodium level
7L1A.11	Dialysis for renal failure
7L1A000	Renal dialysis
7L1A011	Thomas intravascular shunt for dialysis
7L1A100	Peritoneal dialysis
7L1A200	Haemodialysis NEC
7L1A400	Automated peritoneal dialysis
7L1A500	Continuous ambulatory peritoneal dialysis
7L1A600	Peritoneal dialysis NEC
7L1B.11	Placement ambulatory dialysis apparatus - compens renal fail
7L1B000	Insertion of ambulatory peritoneal dialysis catheter
7L1B100	Removal of ambulatory peritoneal dialysis catheter
7L1B200	Flushing of peritoneal dialysis catheter
7L1C000	Insertion of temporary peritoneal dialysis catheter
7L1f000	Extracorporeal albumin haemodialysis
SP01500	Mechanical complication of dialysis catheter
SP05613	[X] Peritoneal dialysis associated peritonitis
SP06B00	Continuous ambulatory peritoneal dialysis associated perit
SP0E.00	Disorders associated with peritoneal dialysis
SP0E000	Bloodstained peritoneal dialysis effluent
SP0E100	Thrombus in peritoneal dialysis catheter
SP0F.00	Haemodialysis first use syndrome
SP0G.00	Anaphylactoid reaction due to haemodialysis
SP3y900	Acute hypercalcaemia of dialysis
TA02.00	Accid cut,puncture,perf,h'ge - kidney dialysis/oth perfusion
TA02000	Accid cut,puncture,perf,h'ge - kidney dialysis
TA02011	Accidental cut/puncture/perf/haem'ge during renal dialysis
TA12000	Foreign object left in body during kidney dialysis
TA12011	Foreign object left in body during renal dialysis
TA22000	Failure of sterile precautions during kidney dialysis
TA22011	Failure of sterile precautions during renal dialysis
TA42000	Mechanical failure of apparatus during kidney dialysis
TA42011	Mechanical failure of apparatus during renal dialysis
TB11.00	Kidney dialysis with complication, without blame
TB11.11	Renal dialysis with complication, without blame
U641.00	[X]Kidny dialysis caus abn reac pt/lat comp no misad at time
Z131400	Warming patient by dialysis therapy

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Z131500	Warming patient with warm haemodialysis
Z131600	Warming patient with warm peritoneal dialysis
Z132800	Cooling patient using cool peritoneal dialysis
Z1A..00	Dialysis training
Z1A1.00	Peritoneal dialysis training
Z1A1.11	PD - Peritoneal dialysis training
Z1A2.00	Haemodialysis training
Z1A2.11	HD - Haemodialysis training
Z919.00	Care of haemodialysis equipment
Z919100	Priming haemodialysis lines
Z919200	Washing back through haemodialysis lines
Z919300	Reversing haemodialysis lines
Z919400	Recirculation of the dialysis machine
Z91A.00	Peritoneal dialysis bag procedure
Z91A100	Putting additive into peritoneal dialysis bag
ZV56.00	[V]Aftercare involving intermittent dialysis
ZV56000	[V]Aftercare involving extracorporeal dialysis
ZV56011	[V]Aftercare involving renal dialysis NOS
ZV56100	[V]Preparatory care for dialysis
ZV56y00	[V]Other specified aftercare involving intermittent dialysis
ZV56y11	[V]Aftercare involving peritoneal dialysis
ZV56z00	[V]Unspecified aftercare involving intermittent dialysis
ZVu3G00	[X]Other dialysis
SP3y800	Dysequilibrium syndrome
OPCS code	Description
M011	Autotransplantation of kidney
M012	Allotransplantation of kidney from live donor
M013	Allotransplantation of kidney from cadaver NEC
M014	Allotransplantation of kidney from cadaver heart beating
M015	Allotransplantation of kidney from cadaver heart non-beating
M018	Other specified transplantation of kidney
M019	Unspecified transplantation of kidney
M026	Excision of rejected transplanted kidney
X401	Renal dialysis
X402	Peritoneal dialysis NEC
X403	Haemodialysis NEC
X404	Haemofiltration
X405	Automated peritoneal dialysis
X406	Continuous ambulatory peritoneal dialysis
X407	Haemoperfusion
X408	Other specified compensation for renal failure
X409	Unspecified compensation for renal failure
ICD10	Description
T861	Kidney transplant failure and rejection
Z940	Kidney transplant status
Y841	Kidney dialysis

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Z491	Extracorporeal dialysis
Z492	Other dialysis
Z992	Dependence on renal dialysis
Y602	During kidney dialysis or other perfusion
Y612	During kidney dialysis or other perfusion
Y622	During kidney dialysis or other perfusion
Z490	Preparatory care for dialysis

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Appendix 3.2: Secondary care referral codes to Nephrology within THIN

nhsspec	speciality	subspec
ABG	General Surgery	Nephrology
AEI	General Medical	Nephrology
AHK	Orthopaedic	Nephrology
AKM	Rheumatology	Nephrology
ANO	Ear Nose & Throat	Nephrology
AQQ	Gynaecology	Nephrology
ATS	Obstetrics	Nephrology
AWU	Paediatrics	Nephrology
AZW	Ophthalmology	Nephrology
BCY	Psychiatry	Nephrology
BGA	Geriatrics	Nephrology
BJC	Dermatology	Nephrology
BME	Neurology	Nephrology
BPG	Genito-Urinary	Nephrology
BSI	X - Ray	Nephrology
BVK	Pathology	Nephrology
BYM	Other	Nephrology
CBO	Non-referral report	Nephrology
CEQ		Nephrology
Medcode	Description	
8H4L.00	Referred to nephrologist	
8HV.a.00	Private referral to nephrologist	
9NNf500	Under care of nephrologist	
ZL18O00	Under care of nephrologist	
ZL5AN00	Referral to nephrologist	
ZL9A000	Seen by nephrologist	
ZLD3O00	Discharge by nephrologist	
9b9H.00	Nephrology	
9N1m.00	Seen in nephrology clinic	
ZLE6M00	Discharge from nephrology service	
9N1m.11	Seen in renal clinic	
9Ni1.00	Did not attend renal clinic	
8H4a.00	Referral to renal physician	

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Appendix 3.3: Additional health data (ahd) codes relating to Laboratory test results

Laboratory variables	ahd code
eGFR ($\mu\text{mol/l}$)	1001400326
Serum creatinine	1001400019
Albumin creatinine ratio (mg/mmol)	1001400319
Hb (g/dl)	1001400027
Calcium (corrected) (mmol/l)	1001400012
Phosphate (mmol/l)	1001400061
Parathyroid hormone (pmol/l)	1001400272
Albumin (g/L)	1001400002
Blood Pressure (mm Hg)	1005010500

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Appendix 3.4: Table of BNF codes relating to the class of medications

BNF code	Drug class
Anti-hypertensive	
02040000	Beta-adrenoceptor blocking drugs
02050000	Hypertension and heart failure
02050100	Vasodilator antihypertensive drugs
02050200	Centrally-acting antihypertensive drugs
02050300	Adrenergic neurone blocking drugs
02050400	Alpha-adrenoceptor blocking drugs
02050500	Drugs affecting the renin-angiotensin system
02050501	Angiotensin-converting enzyme inhibitors
02050502	Angiotensin-II receptor antagonists
02050503	Renin inhibitors
02060200	Calcium channel blockers
Antiplatelet/Anticoagulant	
02080100	Parenteral anticoagulants
02080200	Oral anticoagulants
02090000	Antiplatelet drugs
Lipid-regulating drugs	
02120000	Lipid-regulating drugs
Iron	
09010101	Oral iron
09010102	Parenteral iron
Erythropoietin stimulating agents	
09010300	Drugs used in hypoplastic, haemolytic & renal anaemia
Phosphate binders	
09050202	Phosphate-binding agents

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Appendix 3.5: Codes related to patient consultation locations

Locate code	Description
A	Clinic (often by nurse)
B	Night Visit by Deputising Service conducted by a locum GP - often an emergency. Request for visit made either between 8pm and 7am, at weekends or holidays
C	Follow-up/routine visit
D	Night Visit by Local Rota, conducted by colleague or locum GP - often an emergency. Request for visit made either between 8pm and 7am, at weekends or holidays
E	Mail from Patient
F	Night Visit by Practice Doctor - often an emergency. Request for visit made at weekends or holidays either between 8pm and 7am,
G	Out of Hours visit by Practice Doctor, often an emergency. Request for visit made either between 7-9am or 5-8pm
H	Out of Hours visit by Non-Practice Doctor, examination by a doctor other than the patients GP, often an emergency. Request for visit made either between 7-9am or 5-8 pm
I	Surgery Consultation
J	Telephone Call from Patient
K	Acute Visit by GP to patients home, usually during normal working hours
L	Discharge Details
M	Letter from Outpatients
N	Repeat Issue
O	Other
P	Results Recording
Q	Mail to patient
R	Emergency Consultation
S	Administration
T	Casualty attendance
U	Telephone call to patient
V	Third party consultation
W	Hospital Admission
X	Home visit
Y	Day case report (following surgical procedure in hospital without an overnight stay)
Z	Walk in centre (minor illness & injury treatment ^a not part of GP surgery)
a	Minor injury service (service offered by GP surgery or hospital unit)
b	Community clinic
c	Night visit
d	Co-op surgery consultation (collaborative out-of hours service by local GP ^{Es})
e	Health authority entry
f	Co-op telephone advice (collaborative out-of hours service by local GP ^{Es})
g	Telephone consultation
h	Childrens home visit

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i	Hotel visit
j	Nursing home visit
k	Residential home visit
l	Twilight visit
m	Co-op home visit (collaborative out of hours service by local GPÊs)
n	GOS18 report (referral from optician)
o	NHS direct report
p	Community nursing note
q	Community nursing report
r	Health visitor note
s	Health visitor report
t	Social services report
u	Triage
v	Non-consultation medication data
w	GP to GP communication transaction
x	Non-consultation data
y	ePharmacy message

Appendices

Appendix 4.1: Topic Guide: agreed (Version submitted to the ethics committee)

Background

Perhaps if we could start off with why you have been attending the renal clinic?

Prompts: a. how long? b. what is wrong c. treatment

Patient approach

1. How were you first approached regarding the EQUAL study?

Prompts: 1. where/whom 2. Good/ not so good

2. What influenced your decision to take part/ not take part?

3. Do you have any views on how we should approach people to take part? What would have worked for you?

Prompts: 1. person/phone/ in clinic/written

Information

1. I'm keen to know your thoughts on the information you were given about the equal study when you were approached to take part?

Prompts: 1. Pamphlet/ PIS 2. Did they read it? 3. Sufficient/elaborate/poor/missing 4. Written/verbal/face to face 5. Did it affect your decision? How?

2. Having read the information was it clear to you what was going to happen in the study?

Prompts: 1. Uncertainties about the study

3. Did you have the opportunity ask questions and did the answers bring about more clarity?

4. Were you happy with the way the enrolment appointment went? Was it as you expected?

Decision making

1. How did you come to your decision about whether or not to take part? (Reasons for taking part/not taking part). Which was/ were the most important reasons? Anything in particular that 'put you off'?

Prompts: 1. Any key information that helped type/source/content 2. Decision Easy/difficult; how long did you take deciding? 3. Factors-family etc 4. Aspects of the study 5. Previous experiences 6. Doctor/unit

2. What was your nurse/doctor's reaction about your decision?

3. Would any incentives have influenced your decision to participate in this study?

Prompts: 1. Transport 2. Home visit

Consent

1. Did you understand the process of consent?

Prompts: 1. enough information to consent 2. Different elements of the form 3. Patient rights

Additional demands on the patient: extra procedures and time pressures

1. Were there any commitments and pressures that were contributory to your not participating in this study? **Prompts:** 1. travel distance, travel costs and financial constraints 2. Family duties 3. Medical problems

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2. Was there anything about the study that you thought was too demanding?

Prompts: 1. Frequency of visits 2. Length of the study 3. blood test

Medical research

1. I would be keen to know your views on medical research?

Prompts: 1. Importance 2. How would it help patients in the future(better treatments for other in the future)?

2. Have you had previous experiences of being part of a medical study? If so can you please share these with me?
3. If you were to be approached regarding another study what factors about it would influence whether or not you agreed to take part?
4. Would your decision be different if your doctors approached you to participate in a study or recommended you to participate in the study?

Appendices

Appendix 4.2: Topic Guide: declined (Version submitted to the ethics committee)

Background

Perhaps if we could start off with why you have been attending the renal clinic?

Prompts: a. how long? b. what is wrong c. treatment

Patient approach

1. How were you first approached regarding the EQUAL study?

Prompts: 1. where/whom 2. Good/ not so good

2. What influenced your decision?

3. Do you have any views on how we should approach people to take part? What would have worked for you?

Prompts: 1. person/phone/ in clinic/written

Information

1. I'm keen to know your thoughts on the information you were given about the equal study when you were approached to take part?

Prompts: 1. Pamphlet/ PIS 2. Did they read it? 3. Sufficient/elaborate/poor/missing 4. Written/verbal/face to face 5. Did it affect your decision? How?

2. Having read the information was it clear to you what was going to happen in the study?

Prompts: 1. Uncertainties about the study

3. Did you have the opportunity ask questions and did the answers bring about more clarity?

Decision making

1. How did you come to your decision? (Reasons for taking part/not taking part)

Prompts: 1. Any key information that helped type/source/content 2. Decision Easy/difficult 3. Factors-family etc 4. Aspects of the study 5. Previous experiences 6. Doctor/unit

2. What was your nurse/doctor's reaction about your decision?

3. Would any incentives have influenced your decision to participate in this study?

Prompts: 1. Transport 2. Home visit

Additional demands on the patient: extra procedures and time pressures

1. Were there any commitments and pressures that were contributory to your not participating in this study? **Prompts:** 1. travel distance, travel costs and financial constraints 2. Family duties 3. Medical problems

2. Was there anything about the study that you thought were demanding?

Prompts: 1. Frequency 2. Length of the study 3. Blood test

Medical research

1. I would be keen to know your views on medical research?

Prompts: 1. Importance 2. How would it help patients in the future(better treatments for other in the future)?

2. Have you had previous experiences of being part of a medical study? If so can you please share these with me?

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3. If you were to be approached regarding another study what factors about it would influence your participation/ non-participation?
4. Would your decision be different if your doctors approached you to participate in a study or recommended you to participate in the study?

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Appendix 4.3: Topic Guide: agreed (Final Version)

Background

Perhaps if we could start off with why you have been attending the renal clinic?

Prompts: a. how long? b. what is wrong c. treatment **d. other medical problems e. physical barriers (vision, deafness, memory) f. caring responsibilities**

Patient Activation

1. Are you aware of your health problems and what causes them?
2. If you are not feeling well, what do you do? Do you know when you need to see the doctor and when you can take care of your own health problems?
3. When you see the doctor, if something is bothering you regarding your health do you tell, the doctor of this even if he/she do not ask?
4. Do you know what each of your tablets do?
5. Do you know what treatments are available for your health problems? eg kidney failure
6. Do you take over the counter remedies for your health if required?
7. Do you know of life style measures for your health problems? Diet? Exercise?
8. **To explore awareness of medical problems and impact of medical problems**

Patient approach

4. How were you first approached regarding the EQUAL study?
Prompts: 1. where/whom 2. Good/ not so good
5. What influenced your decision to take part/ not take part?
Explore around Altruism and perceived personal benefit gained.
6. Do you have any views on how we should approach people to take part? What would have worked for you?
Prompts: 1. person/phone/ in clinic/written

Information

5. I'm keen to know your thoughts on the information you were given about the equal study when you were approached to take part?
Prompts: 1.Aims and objectives of the study 2. Pamphlet/ PIS 3. Did they read it? 4. Any terminology that stood out (CKD, kidney disease and percentage).5. Sufficient/elaborate/poor/missing 6. Written/verbal/face to face 7. Did it affect your decision? How?
6. Having read the information was it clear to you what was going to happen in the study?
Prompts: 1. Uncertainties about the study
7. Did you have the opportunity ask questions and did the answers bring about more clarity?
8. Were you happy with the way the enrolment appointment went? Was it as you expected?

Decision making

4. How did you come to your decision about whether or not to take part? (Reasons for taking part/not taking part). Which was/ were the most important reasons? Anything in particular that 'put you off'?

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- Prompts:** 1. Any key information that helped type/source/content 2. Decision Easy/difficult; how long did you take deciding? 3. Factors-family etc 4. Aspects of the study 5. Previous experiences 6. Doctor/unit
5. What was your nurse/doctor's reaction about your decision?
 6. Would any incentives have influenced your decision to participate in this study?

Prompts: 1. Transport 2. Home visit

Consent

2. Did you understand the process of consent?
Prompts: 1. enough information to consent 2. Different elements of the form 3. Patient rights

Additional demands on the patient: extra procedures and time pressures

3. Were there any commitments and pressures that were contributory to your not participating in this study? **Prompts:** 1. travel distance, travel costs and financial constraints 2. Family duties 3. Medical problems
4. Was there anything about the study that you thought was too demanding?
Prompts: a. Frequency of visits b. Length of the study c. blood test

Medical research

5. I would be keen to know your views on medical research?
Prompts: 1. Importance 2. How would it help patients in the future (better treatments for other in the future)?
 6. Have you had previous experiences of being part of a medical study? If so can you please share these with me?
 7. If you were to be approached regarding another study what factors about it would influence whether or not you agreed to take part?
- Would your decision be different if your doctors approached you to participate in a study or recommended you to participate in the study?

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Appendix 4.4: Topic Guide: declined (Final version)

Background

Perhaps if we could start off with why you have been attending the renal clinic?

Prompts: a. how long? b. what is wrong c. treatment **d. other medical problems e. physical barriers (vision, deafness, memory) f. caring responsibilities**

Patient Activation

9. Are you aware of your health problems and what causes them?
10. If you are not feeling well, what do you do? Do you know when you need to see the doctor and when you can take care of your own health problems?
11. When you see the doctor, if something is bothering you regarding your health do you tell, the doctor of this even if he/she do not ask?
12. Do you know what each of your tablets do?
13. Do you know what treatments are available for your health problems? eg kidney failure
14. Do you take over the counter remedies for your health if required?
15. Do you know of life style measures for your health problems? Diet? Exercise?
16. **To explore awareness of medical problems and impact of medical problems**

Patient approach

7. How were you first approached regarding the EQUAL study?

Prompts: 1. where/whom 2. Good/ not so good

8. What influenced your decision?

Explore around Altruism

9. Do you have any views on how we should approach people to take part? What would have worked for you?

Prompts: 1. person/phone/ in clinic/written

Information

9. I'm keen to know your thoughts on the information you were given about the equal study when you were approached to take part?
10. **Prompts: 1.Aims and objectives of the study 2. Pamphlet/ PIS 3. Did they read it? 4. Any terminology that stood out (CKD, kidney disease and percentage).5. Sufficient/elaborate/poor/missing 6. Written/verbal/face to face 7. Did it affect your decision? How?**
11. Having read the information was it clear to you what was going to happen in the study?
Prompts: 1. Uncertainties about the study
12. Did you have the opportunity ask questions and did the answers bring about more clarity?

Decision making

7. How did you come to your decision? (Reasons for taking part/not taking part)
Prompts: 1. Any key information that helped type/source/content 2. Decision Easy/difficult 3. Factors-family etc 4. Aspects of the study 5. Previous experiences 6. Doctor/unit
8. What was your nurse/doctor's reaction about your decision?

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9. Would any incentives have influenced your decision to participate in this study?

Prompts: 1. Transport 2. Home visit

Additional demands on the patient: extra procedures and time pressures

5. Were there any commitments and pressures that were contributory to your not participating in this study? **Prompts:** 1. travel distance, travel costs and financial constraints 2. Family duties 3. Medical problems
6. Was there anything about the study that you thought were demanding?

Prompts: 1. Frequency 2. Length of the study 3. Blood test

Medical research

8. I would be keen to know your views on medical research?
Prompts: 1. Importance 2. How would it help patients in the future(better treatments for other in the future)?
9. Have you had previous experiences of being part of a medical study? If so can you please share these with me?
10. If you were to be approached regarding another study what factors about it would influence your participation/ non-participation?
11. Would your decision be different if your doctors approached you to participate in a study or recommended you to participate in the study?

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Appendix 5.1: Search strategy for systematic review

Chronic Kidney Disease (CKD):

exp renal insufficiency, chronic/

exp Cardiovascular Diseases/ep [Epidemiology]

kidney disease*.ti,ab.

renal disease*.ti,ab.

kidney insufficienc*.ti,ab.

renal insufficienc*.ti,ab.

kidney failure .ti,ab.

kidney dysfunction*.ti,ab.

renal dysfunction*.ti,ab.

kidney impairment*.ti,ab.

renal impairment*.ti,ab.

impaired kidney function*.ti,ab.

impaired renal function*.ti,ab.

decreased kidney function*.ti,ab.

decreased renal function*.ti,ab.

chronic kidney.ti,ab.

chronic renal.ti,ab.

CKD.ti,ab.

CRD.ti,ab.

ESRD.ti,ab.

ESKD.ti,ab.

CKF.ti,ab.

Cohort:

exp cohort studies/

cohort*.pt,ti,ab.

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Longitudinal*.pt,ti,ab.

Follow-up*.pt,ti,ab.

Follow up*.pt,ti,ab.

Prospective* .pt,ti,ab.

Retrospective* .pt,ti,ab.

Observational* .pt,ti,ab.

Elderly:

exp Aged/

elder* .ti,ab.

Older .ti,ab.

Oldest .ti,ab.

old age .ti,ab.

old people .ti,ab.

Geriatric .ti,ab.

Aging .ti,ab.

Ageing .ti,ab.

Frail .ti,ab.

community dwelling .ti,ab.

nursing home .ti,ab.

home for the aged .ti,ab.

homes for the aged .ti,ab.

Residents .ti,ab.

Mortality:

mortality/ or *"cause of death"/ or *fatal outcome/ or *hospital mortality/ or *mortality, premature/ or *survival rate/

exp Renal Insufficiency, Chronic/mo [Mortality]

Europe:

1. exp Europe/

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2. UK.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
3. United Kingdom.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
4. England.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
5. English.mp.
6. (Austria or Austrian).mp.
7. Belgium*.mp.
8. Albania*.mp.
9. Estonia*.mp.
10. Latvia*.mp.
11. Lithuania*.mp.
12. Bosnia*-Herzegovina*.mp.
13. Bulgaria*.mp.
14. Croat*.mp.
15. Hungarian*.mp.
16. Hungary.mp.
17. Macedonia*.mp.
18. (Moldova or Moldavian* or Moldovan).mp.
19. Montenegr*.mp.
20. (Poland or Polish or Pole*).mp.
21. Belarus*.mp.
22. Romania*.mp.
23. Russia*.mp.
24. Serbia*.mp.
25. Slovak*.mp.
26. Sloven*.mp.
27. Ukrain*.mp.

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28. Yugoslavia*.mp.
29. (Finland or Finns or Finn or Finnish).mp.
30. (France or French).mp.
31. German*.mp.
32. (Great Britain or Great British).mp.
33. (Northern Ireland or Northern Irish).mp.
34. (Greece or Greek).mp.
35. Iceland*.mp.
36. (Ireland or Irish).mp.
37. (Italy or Italian*).mp.
38. Luxembourg*.mp.
39. (Netherlands or Dutch).mp.
40. (Portugal or Portuguese).mp.
41. (Denmark or Danish).mp.
42. (Norway or Norwegian*).mp.
43. (Sweden or Swedish).mp.
44. (Spain or Spanish).mp.
45. (Switzerland or Swiss).mp.
46. Armenia*.mp.
47. Azerbaijan*.mp.
48. Georgia*.mp.
49. (Turkey or Turkish).mp.
50. (Malta or Maltese).mp.
51. Ulster.mp.
52. Belgian*.mp.
53. Andorra*.mp.
54. (Cyprus or Cypriot*).mp.
55. Czech*.mp.
56. (Kazakhstan or Kazakh*).mp.

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57. Liechtenstein*.mp.
58. (Monaco or Monacian* or Monegasque*).mp.
59. (San Marino or Sammarinese*).mp.
60. (Vatican or Vanticanian*).mp.

America:

1. exp North America/
2. Canada.mp.
3. (US or USA).mp.
4. United States.mp.
5. America*.mp.
6. (Alabama or Alaska or Arizona or Arkansas or California or Colorado or Connecticut or Delaware or Florida or Georgia or Hawaii or Idaho or Illinois or Indiana or Iowa or Kansas or Kentucky or Louisiana or Maine or Maryland or Massachusetts or Michigan or Minnesota or Mississippi or Missouri or Montana or Nebraska or Nevada or New Hampshire or New Jersey or New Mexico or New York or North Carolina or North Dakota or Ohio or Oklahoma or Oregon or Pennsylvania or Rhode Island or South Carolina or South Dakota or Tennessee or Texas or Utah or Vermont or Virginia or Washington or West Virginia or Wisconsin or Wyoming).ti,ab.

Limits:

English language

PY(Publication Year):

Time period 1/1/2002 to 31/12/2013

PT (Publication Type):

Deselect conference papers and other publication types which will not use STROBE guidance for reporting (e. letter to the editor)

(autobiography or biography or case reports or clinical conference or clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial or congresses or consensus development conference or consensus development conference, nih or controlled clinical trial or dictionary or directory or editorial or in vitro or interactive tutorial or interview or lectures or legal

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cases or legislation or letter or news or newspaper article or patient education handout or portraits or randomized controlled trial or video-audio media or webcasts)

Selection of human studies:

Animals/ not humans/

Not previous

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Appendix 5.2: STROBE scoring sheet

Original STROBE Item No.	STROBE Description	Rules/Explanatory notes	Answer choices				
			yes	partly	no	unclear	not applicable
Title and Abstract							
1a	Is the design described adequately in the title or abstract?	If the study design was not specifically stated, this should be recorded as not being complete.					
1b	Does the abstract provide an informative summary of what was done and found?	The abstract provides key information that enables readers to understand a study and decide whether to read the article and should only present information that is provided in the article.					
Introduction							
2	Is the scientific background and rationale for the investigation reported?	The paper should give an overview of what is known on a topic and what gaps in current knowledge are addressed by the study.					
3a	Are any pre-specified hypotheses reported?	Objectives are the detailed aims of the study. Well-crafted objectives specify populations, exposures and outcomes, and parameters that will be estimated.					
3b	Are the objectives reported?						
Methods							
4	Are the key elements (i.e., retrospective/prospective, cohort/cross-sectional) of the study design presented early in the paper?	For example, authors should indicate that the study was a cohort study, which followed people over a particular time period and describes the group of persons that comprised the cohort and their exposure status. Authors should refrain from simply calling a study 'prospective' or 'retrospective' because these terms are ill-defined					
5a	Are the settings reported?	Studies that did not report the setting or locations but referred readers to a previous publication should be considered as inconsistent with complete reporting. Readers need information on setting and locations to assess the context and generalisability of a study's results.					
5b	Are the locations reported?						
5c	Are relevant dates including periods of recruitment reported?	Authors should state dates rather than only describing the length of time periods. If the dates of recruitment were recorded anywhere in the article (not necessarily in the "Methods" section), the corresponding item should be rated as complete.					
5d	Are relevant dates including periods of exposure reported?						
5e	Are relevant dates including periods of follow-up reported?						
5f	Are relevant dates including periods of data collection reported?						
6a	Are the eligibility criteria for participants described?	Detailed descriptions of the study participants help readers understand the applicability of the results. Clinical, demographic and other characteristics of					
6b	Are the sources of participants described?						

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6c	Are the methods of selection described?	eligible participants should be described. Eligibility criteria may be presented as inclusion and exclusion criteria.				
6d	Are the methods of follow-up described?	Knowing details about follow-up procedures, including whether procedures minimised nonresponse and loss to follow-up and whether the procedures were similar for all participants, informs judgments about the validity of results.				
6e	If it is a matched study, are the matching criteria and the numbers of exposed and unexposed described?	Because matching can be done in various ways, with one or more controls per case, the rationale for the choice of matching variables and the details of the method used should be described. To allow readers to judge whether the matched design was appropriately taken into account in the analysis, we recommend that authors describe in detail what statistical methods were used to analyse the data.				
7a	Are all outcomes described if applicable?	Disease outcomes require an adequately detailed description of the diagnostic criteria.				
7b	Are all exposures described if applicable?					
7c	Are all predictors described if applicable?					
7d	Are potential confounders described?					
7e	Are all effect modifiers described?	Authors should declare all 'candidate variables' considered for statistical analysis, rather than selectively reporting only those included in the final models				
7f	Are diagnostic criteria described if applicable?					
8a	Are the sources of data and details of methods of measurement given for each variable of interest?	The way in which exposures, confounders and outcomes were measured affects the reliability and validity of a study. Measurement error and misclassification of exposures alternatively, outcomes can make it more difficult to detect cause-effect relationships or may produce spurious relationships.				
8b	If there is more than 1 group, are the measurement methods comparable?					
9	Was there any effort to address potential sources of bias?	Authors should have made attempts to address sources of bias if they incorporated any tools to do this, e.g., using standardised definitions or validated scoring systems should be rated as complete. Addressing sources of bias should never be considered "not applicable" in an observational study.				
10	Did they describe how the study size was determined?	The importance of sample size determination in observational studies depends on the context. Investigators should report pertinent formal sample size calculations if they were done.				
11a	Did they describe how quantitative variables were handled in the analysis?	Authors should explain why and how they grouped quantitative data, including the number of categories, the cut-points, and category mean or median values. Whenever data are reported in tabular form, the counts of cases, controls, persons at risk, person-time at risk, etc. should be given for				
11b	Did they describe which groupings were chosen for quantitative variables?					

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11c	Did they describe why quantitative groups were chosen?	each category. Tables should not consist solely of effect-measure estimates or results of model fitting.					
12a	Did they describe all statistical methods including those to deal with confounding?	In relation to statistical methods, unless authors state which confounders were adjusted for and why, should not be rated as complete. Authors should clarify reasons for particular analyses.					
12b	Did they describe methods to examine subgroups and interactions?	Readers need to know which subgroup analyses were planned in advance, and which arose while analysing the data.					
12c	Did they explain how missing data was addressed?	Authors should report the number of missing values for each variable of interest (exposures, outcomes, confounders) and for each step in the analysis. Authors should give reasons for missing values if possible, and indicate how many individuals were excluded because of missing data when describing the flow of participants through the study.					
12d	Did they explain if applicable how losses to follow-up were addressed?	Authors to report how many patients were lost to follow-up and what censoring strategies they used.					
12e	Did they describe any sensitivity analysis?	Sensitivity analyses are useful to investigate whether or not the main results are consistent with those obtained with alternative analysis strategies or assumptions					
Results							
13a	Did they report the numbers of individuals at each stage of the study numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, and completed follow-up and were analysed?	Those included in a study often differ in relevant ways from the target population to which results are applied. This may result in estimates of prevalence or incidence that do not reflect the experience of the target population.					
13b	Did they give reasons for nonparticipation at each stage? ^a	Explaining the reasons why people no longer participated in a study or why they were excluded from statistical analyses helps readers judge whether the study population was representative of the target population and whether bias was possibly introduced.					
13c	Did they use a flow diagram if appropriate?						
14a	Did they give the characteristics of study participants (e.g., demographic, clinical, and social) and information on exposures and potential confounders?	Readers need descriptions of study participants and their exposures to judge the generalisability of the findings. Information about potential confounders, including whether and how they were measured, influences judgments about study validity. Authors should give the mean and Standard deviation, or when the data have an asymmetrical distribution, as is often the case, the median and percentile range (e.g., 25th and 75th percentiles).					
14b	Did they indicate the number of participants with missing data for each variable of interest?	As missing data may bias or affect the generalisability of results, authors should tell readers amounts of missing data for exposures, potential confounders, and other important characteristics of patients. Should also include the extent of loss to follow-up.					
14c	Did they summarise follow-up time (average and total amount)?	Readers need to know the duration and extent of follow-up for the available outcome data.					
15a	Did they report numbers of outcome measures over	Authors should report the numbers of events for each outcome of interest.					

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	time?	Consider reporting the event rate per person-year of follow-up. If the risk of an event changes over follow-up time, present the numbers and rates of events in appropriate intervals of follow-up or as a Kaplan-Meier life table or plot.					
15b	Did they report summary measures over time?						
16a	Did they give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval)?	Readers can compare unadjusted measures of association with those adjusted for potential confounders and judge by how much, and in what direction, they changed.					
16b	Did they detail which confounders were adjusted for and why they were included?	Authors should explain all potential confounders considered and the criteria for excluding or including variables in statistical models. Decisions about excluding or including variables should be guided by knowledge, or explicit assumptions, on causal relations.					
16c	Did they report category boundaries when continuous variables were categorized?	Authors should report the category boundaries, and report the range of the data and the mean or median values within categories.					
16d	Did they, if relevant, consider translating estimates of relative risk into absolute risk for a meaningful period?	It was only appropriate to translate relative risk into absolute risk if there was convincing evidence of a causal association.					
17a	Did they report on other analyses done, e.g., analysis of subgroups or interactions?	Authors should report which analyses were planned, and which were not. This will allow readers to judge the implications of multiplicity, taking into account the study's position on the continuum from discovery to verification or refutation.					
17b	Did they do a sensitivity analysis?	Sensitivity analyses are helpful to investigate the influence of choices made in the statistical analysis, or to investigate the robustness of the findings to missing data or possible biases.					
Discussion							
18	Did they summarise key results concerning study objectives?	The short summary reminds readers of the main findings and may help them assess whether the subsequent interpretation and implications offered by the authors are supported by the findings.					
19	Did they discuss the limitations of the study taking into account potential sources of bias or imprecision (including discussion of the magnitude of any potential sources of bias)?	Authors should identify the sources of bias and confounding that could have affected results, but also to discuss the relative importance of different biases, including the likely direction and magnitude of any potential bias. Authors may compare the study being presented with other studies in the literature regarding validity, generalisability and precision. In this approach, each study can be viewed as a contribution to the literature, not as a stand-alone basis for inference and action.					
20	Did they give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence?	Authors should consider potential sources of bias, including loss to follow-up and non-participation. Due consideration should be given to confounding, the results of relevant sensitivity analyses, and to the issue of multiplicity and subgroup analyses. Authors should also consider residual confounding due to unmeasured variables or imprecise measurement of confounders. Authors should put their results in context with similar studies and explain					

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		how the new study affects the existing body of evidence, by referring to a systematic review.					
21	Did they discuss the generalisability (external validity) of the study results?	Can results be applied to an individual, groups or populations that differ from those enrolled in the study with regard to age, sex, ethnicity, the severity of disease, and co-morbid conditions? Are the nature and level of exposures comparable, and the definitions of outcomes relevant to another setting or population? Are results from health services research in one country applicable to health systems in other countries?					
Other Information							
22a	Did they give the source of the funding in the present study and, if applicable, for the original study on which the present article is based?						
22b	Did they give the role of the funders in the present study and, if applicable, for the original study on which the present article is based?	Unless the role of the funders was specifically stated, this should not be recorded as complete.					

^a For studies based on disease registries or databases, a number of the checklist items are not applicable, e.g., the dates of recruitment, numbers eligible at each stage of the study, reasons for nonparticipation, or flow diagrams

The number and proportion of reported items (“yes” & “partly” responses) and not reported items (all responses except “yes”, “partly” or “not applicable”) will be analysed for each study

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Appendix 5.3: Newcastle-Ottawa Quality Assessment Scale for cohort studies

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and

Outcome categories. A maximum of two stars can be given for Comparability

Selection

- 1) Representativeness of the exposed cohort
 - a) truly representative of the average _____ (describe) in the community *
 - b) somewhat representative of the average _____ in the community *
 - c) selected group of users eg nurses, volunteers
 - d) no description of the derivation of the cohort
- 2) Selection of the non exposed cohort
 - a) drawn from the same community as the exposed cohort *
 - b) drawn from a different source
 - c) no description of the derivation of the non exposed cohort
- 3) Ascertainment of exposure
 - a) secure record (eg surgical records) *
 - b) structured interview *
 - c) written self report
 - d) no description
- 4) Demonstration that outcome of interest was not present at start of study
 - a) yes *
 - b) no

Comparability


- 1) Comparability of cohorts on the basis of the design or analysis
 - a) study controls for _____ (select the most important factor) *
 - b) study controls for any additional factor * (This criteria could be modified to indicate specific control for a second important factor.)

Outcome

- 1) Assessment of outcome
 - a) independent blind assessment *
 - b) record linkage *
 - c) self report
 - d) no description
- 2) Was follow-up long enough for outcomes to occur
 - a) yes (select an adequate follow up period for outcome of interest) *
 - b) no
- 3) Adequacy of follow up of cohorts
 - a) complete follow up - all subjects accounted for *
 - b) subjects lost to follow up unlikely to introduce bias - small number lost - > ____ % (select an adequate %) follow up, or description provided of those lost) *
 - c) follow up rate < ____% (select an adequate %) and no description of those lost
 - d) no statement

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Appendix 5.4: Scottish Intercollegiate Guidelines Network (SIGN) checklist for cohort studies

 SIGN	Methodology Checklist 3: Cohort studies		
Study identification (<i>Include author, title, year of publication, journal title, pages</i>)			
Guideline topic:		Key Question No:	Reviewer:
<p>Before completing this checklist, consider:</p> <ol style="list-style-type: none"> 1. Is the paper really a cohort study? If in doubt, check the study design algorithm available from SIGN and make sure you have the correct checklist. 2. Is the paper relevant to key question? Analyse using PICO (Patient or Population Intervention Comparison Outcome). IF NO REJECT (give reason below). IF YES complete the checklist.. 			
Reason for rejection: 1. Paper not relevant to key question <input type="checkbox"/> 2. Other reason <input type="checkbox"/> (please specify):			
Please note that a retrospective study (ie a database or chart study) cannot be rated higher than +.			
<i>Section 1: Internal validity</i>			
<i>In a well conducted cohort study:</i>			Does this study do it?
1.1	The study addresses an appropriate and clearly focused question.	Yes <input type="checkbox"/> No <input type="checkbox"/> Can't say <input type="checkbox"/>	
SELECTION OF SUBJECTS			
1.2	The two groups being studied are selected from source populations that are comparable in all respects other than the factor under investigation.	Yes <input type="checkbox"/> No <input type="checkbox"/> Can't say <input type="checkbox"/> Does not apply <input type="checkbox"/>	
1.3	The study indicates how many of the people asked to take part did so, in each of the groups being studied.	Yes <input type="checkbox"/> No <input type="checkbox"/> Does not apply <input type="checkbox"/>	
1.4	The likelihood that some eligible subjects might have the outcome at the time of enrolment is assessed and taken into account in the analysis.	Yes <input type="checkbox"/> No <input type="checkbox"/> Can't say <input type="checkbox"/> Does not apply <input type="checkbox"/>	

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1.5	What percentage of individuals or clusters recruited into each arm of the study dropped out before the study was completed.	
1.6	Comparison is made between full participants and those lost to follow up, by exposure status.	Yes <input type="checkbox"/> No <input type="checkbox"/> Can't say <input type="checkbox"/> Does not apply <input type="checkbox"/>
ASSESSMENT		
1.7	The outcomes are clearly defined.	Yes <input type="checkbox"/> No <input type="checkbox"/> Can't say <input type="checkbox"/>
1.8	The assessment of outcome is made blind to exposure status. If the study is retrospective this may not be applicable.	Yes <input type="checkbox"/> No <input type="checkbox"/> Can't say <input type="checkbox"/> Does not apply <input type="checkbox"/>
1.9	Where blinding was not possible, there is some recognition that knowledge of exposure status could have influenced the assessment of outcome.	Yes <input type="checkbox"/> No <input type="checkbox"/> Can't say <input type="checkbox"/> <input type="checkbox"/>
1.10	The method of assessment of exposure is reliable.	Yes <input type="checkbox"/> No <input type="checkbox"/> Can't say <input type="checkbox"/>
1.11	Evidence from other sources is used to demonstrate that the method of outcome assessment is valid and reliable.	Yes <input type="checkbox"/> No <input type="checkbox"/> Can't say <input type="checkbox"/> Does not apply <input type="checkbox"/>
1.12	Exposure level or prognostic factor is assessed more than once.	Yes <input type="checkbox"/> No <input type="checkbox"/> Can't say <input type="checkbox"/> Does not apply <input type="checkbox"/>
CONFOUNDING		
1.13	The main potential confounders are identified and taken into account in the design and analysis.	Yes <input type="checkbox"/> No <input type="checkbox"/> Can't say <input type="checkbox"/>
STATISTICAL ANALYSIS		
1.14	Have confidence intervals been provided?	Yes <input type="checkbox"/> No <input type="checkbox"/>

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SECTION 2: OVERALL ASSESSMENT OF THE STUDY						
2.1	How well was the study done to minimise the risk of bias or confounding?	High quality (++) <input type="checkbox"/> Acceptable (+) <input type="checkbox"/> Unacceptable – reject 0				
2.2	Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, do you think there is clear evidence of an association between exposure and outcome?	<table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 50%; padding: 5px;">Yes <input type="checkbox"/></td> <td style="width: 50%; padding: 5px;">No <input type="checkbox"/></td> </tr> <tr> <td style="padding: 5px;">Can't say <input type="checkbox"/></td> <td></td> </tr> </table>	Yes <input type="checkbox"/>	No <input type="checkbox"/>	Can't say <input type="checkbox"/>	
Yes <input type="checkbox"/>	No <input type="checkbox"/>					
Can't say <input type="checkbox"/>						
2.3	Are the results of this study directly applicable to the patient group targeted in this guideline?	<table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 50%; padding: 5px;">Yes <input type="checkbox"/></td> <td style="width: 50%; padding: 5px;">No <input type="checkbox"/></td> </tr> </table>	Yes <input type="checkbox"/>	No <input type="checkbox"/>		
Yes <input type="checkbox"/>	No <input type="checkbox"/>					
2.4	Notes. Summarise the authors conclusions. Add any comments on your own assessment of the study, and the extent to which it answers your question and mention any areas of uncertainty raised above.					

Appendix 5.5: Critical Appraisal Skills Programme (CASP) cohort checklist

Making sense of evidence about clinical effectiveness



12 questions to help you make sense of cohort study

General comments

Three broad issues need to be considered when appraising a cohort study.

Are the results of the study valid? What are the results?

Will the results help locally?

The 12 questions on the following pages are designed to help you think about these issues systematically.

- The first two questions are screening questions and can be answered quickly. If the answer to those two is "yes", it is worth proceeding with the remaining questions.
- There is a fair degree of overlap between several of the questions.
- You are asked to record a "yes", "no" or "can't tell" to most of the questions.
- A number of italicised hints are given after each question. These are designed to remind you why the question is important. There will not be time in the small groups to answer them all in detail!.

A Are the results of the study valid? Screening Questions

<p>1 Did the study address a clearly focused issue? <i>HINT: A question can be focused in terms of?</i></p> <ul style="list-style-type: none"> • <i>the population studied</i> • <i>the risk factors studied</i> • <i>the outcomes considered</i> • <i>is it clear whether the study tried to detect a beneficial or harmful effect?</i> 	<p>Yes D</p>	<p>Can't tell D</p>	<p>No D</p>
<p>2 Did the authors use an appropriate method to answer their question? <i>HINT: Consider</i></p> <ul style="list-style-type: none"> • <i>is a cohort study a good way of answering the question under the circumstances?</i> • <i>did it address the study question?</i> 	<p>Yes D</p>	<p>Can't tell D</p>	<p>No D</p>

Is it worth continuing?

Detailed Questions

<p>3 Was the cohort recruited in an acceptable way?</p> <p><i>HINT: We are looking for selection bias which might compromise the generalisability of the findings:</i></p> <ul style="list-style-type: none"> • <i>Was the cohort representative of a defined population?</i> • <i>Was there something special about the cohort?</i> • <i>Was everybody included</i> • <i>who should have been included?</i> 	<p>Yes D</p>	<p>Can't tell D</p>	<p>No D</p>
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<p>4 Was the exposure accurately measured to minimize bias?</p> <p><i>HINT: We are looking for measurement or classification bias:</i></p> <ul style="list-style-type: none"> • Did they use subjective or objective measurements? • Do the measures truly reflect what you want them to (have they been validated)? • Were all the subjects classified into exposure groups using the same procedure? 	<p>Yes D</p>	<p>Can't tell D</p>	<p>No D</p>
<p>5. Was the outcome accurately measured to minimize bias?</p> <p><i>HINT: We are looking for measurement or classification bias:</i></p> <ul style="list-style-type: none"> • Did they use subjective or objective measurements? • Do the measures truly reflect what you want them to (have they been validated)? • Has a reliable <u>system</u> been established for detecting all the cases (for measuring disease occurrence)? • Were the measurement methods similar in the different groups? • Were the subjects and/or the outcome assessor blinded to exposure (does this matter)? 	<p>Yes D</p>	<p>Can't tell D</p>	<p>No D</p>
<p>6</p> <p>A. Have the authors identified all important confounding factors?</p> <p>List the ones you think might be important, that the author missed.</p> <p>B. Have they taken account of the confounding factors in the design and/or analysis?</p> <p>List:</p> <p><i>HINT:</i></p> <ul style="list-style-type: none"> • Look for restriction in design, and techniques eg modelling, stratified-, regression-, or sensitivity analysis to correct, control or adjust for confounding factors 	<p>Yes D</p>	<p>Can't tell D</p>	<p>No D</p>

<p>A. Was the follow up of subjects complete enough?</p>	<p>Yes D</p>		<p>Can't tell D</p>	<p>No D</p>
<p>B. Was the follow up of subjects long enough?</p>	<p>Yes D</p>		<p>Can't tell D</p>	<p>No D</p>
<p>HINT:</p> <ul style="list-style-type: none"> • <i>The good or bad effects should have had long enough to reveal themselves</i> • <i>The persons that are lost to follow-up may have different outcomes than those available for assessment</i> • <i>In an open or dynamic cohort, was there anything special about the outcome of the people leaving, or the exposure of the people entering the cohort?</i> 				

B What are the results?

<p>8 What are the results of this study?</p> <p>HINT:</p> <ul style="list-style-type: none"> • <i>What are the bottom line results?</i> • <i>Have they reported the rate or the proportion between the exposed/unexposed, the ratio/the rate difference?</i> • <i>How strong is the association between exposure and outcome (RR,)?</i> • <i>What is the absolute risk reduction (ARR)?</i> 				
<p>9. How precise are the results?</p> <p>HINT:</p> <ul style="list-style-type: none"> • <i>Size of the confidence intervals</i> 				
<p>10. Do you believe the results?</p> <p>HINT:</p> <ul style="list-style-type: none"> • <i>Big effect is hard to ignore!</i> • <i>Can it be due to bias, chance or confounding?</i> • <i>Are the design and methods of this study sufficiently flawed to make the results unreliable?</i> • <i>Consider Bradford Hills criteria (eg time sequence, dose-response gradient, biological plausibility, consistency).</i> 	<p>Yes D</p>		<p>Can't tell D</p>	<p>No D</p>

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C Will the results help me locally?

<p>11. Can the results be applied to the local population?</p> <p><i>HINT: Consider whether</i></p> <ul style="list-style-type: none"> • <i>The subjects covered in the study could be sufficiently different from your population to cause concern</i> • <i>Your local setting is likely to differ much from that of the study</i> • <i>Can you quantify the local benefits and harms?</i> 	<p>Yes D</p>	<p>Can't tell D</p>	<p>No D</p>
<p>12. Do the results of this study fit with other available evidence?</p>	<p>Yes D</p>	<p>Can't tell D</p>	<p>No D</p>

One observational study rarely provides sufficiently robust evidence to recommend changes to clinical practice or within health policy decision making. However, for certain questions observational studies provide the only evidence. Recommendations from observational studies are always stronger when supported by other evidence.

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Appendix 5.6: List of articles included for the systematic review by date of publication

1. Fried LF, Shlipak MG, Crump C, et al. Renal insufficiency as a predictor of cardiovascular outcomes and mortality in elderly individuals. *Journal of the American College of Cardiology*. 2003;41:1364-1372.
2. Drey N, Roderick P, Mullee M, Rogerson M. A population-based study of the incidence and outcomes of diagnosed chronic kidney disease. *American Journal of Kidney Diseases*. 2003;42:677-684.
3. Foley RN, Murray AM, Li S, et al. Chronic Kidney Disease and the Risk for Cardiovascular Disease, Renal Replacement, and Death in the United States Medicare Population, 1998 to 1999. *Journal of the American Society of Nephrology*. 2005;16:489-495.
4. Shlipak MG, Fried LF, Cushman M, et al. Cardiovascular mortality risk in chronic kidney disease: Comparison of traditional and novel risk factors. *JAMA*. 2005;293:1737-1745.
5. Fried LF, Katz R, Sarnak MJ, et al. Kidney Function as a Predictor of Noncardiovascular Mortality. *Journal of the American Society of Nephrology*. 2005;16:3728-3735.
6. O'Hare AM, Bertenthal D, Covinsky KE, et al. Mortality Risk Stratification in Chronic Kidney Disease: One Size for All Ages? *Journal of the American Society of Nephrology*. 2006;17:846-853.
7. Hallan SI, Dahl K, Oien CM, et al. Screening strategies for chronic kidney disease in the general population: follow-up of cross sectional health survey. *BMJ*. 2006;333:1047.
8. Wong CF, McCarthy M, Howse MLP, Williams PS. Factors Affecting Survival in Advanced Chronic Kidney Disease Patients Who Choose Not to Receive Dialysis. *Renal Failure*. 2007;29:653-659.
9. O'Hare AM, Choi AI, Bertenthal D, et al. Age Affects Outcomes in Chronic Kidney Disease. *Journal of the American Society of Nephrology*. 2007;18:2758-2765.
10. De Biase V, Tobaldini O, Boaretti C, et al. Prolonged conservative treatment for frail elderly patients with end-stage renal disease: the Verona experience. *Nephrology Dialysis Transplantation*. 2008;23:1313-1317.
11. Hallan S, Astor B, Romundstad S, Aasarød K, Kvenild K, Coresh J. Association of kidney function and albuminuria with cardiovascular mortality in older vs younger individuals: The hunt ii study. *Archives of Internal Medicine*. 2007;167:2490-2496.
12. Pizzarelli F, Lauretani F, Bandinelli S, et al. Predictivity of survival according to different equations for estimating renal function in community-dwelling elderly subjects. *Nephrology Dialysis Transplantation*. 2009;24:1197-1205.
13. Nitsch D, Mylne A, Roderick PJ, Smeeth L, Hubbard R, Fletcher A. Chronic kidney disease and hip fracture-related mortality in older people in the UK. *Nephrology Dialysis Transplantation*. 2009;24:1539-1544.

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14. Snyder JJ, Collins AJ. Association of Preventive Health Care with Atherosclerotic Heart Disease and Mortality in CKD. *Journal of the American Society of Nephrology*. 2009;20:1614-1622.
15. Roderick PJ, Atkins RJ, Smeeth L, et al. CKD and Mortality Risk in Older People: A Community-Based Population Study in the United Kingdom. *American Journal of Kidney Diseases*. 2009;53:950-960.
16. Seyfarth M, Kastrati A, Mann JFE, et al. Prognostic Value of Kidney Function in Patients With ST-Elevation and Non-ST-Elevation Acute Myocardial Infarction Treated With Percutaneous Coronary Intervention. *American Journal of Kidney Diseases*. 2009;54:830-839.
17. Carson RC, Juszczak M, Davenport A, Burns A. Is Maximum Conservative Management an Equivalent Treatment Option to Dialysis for Elderly Patients with Significant Comorbid Disease? *Clinical Journal of the American Society of Nephrology*. 2009;4:1611-1619.
18. El-Ghoul B, Elie C, Sqalli T, et al. Nonprogressive Kidney Dysfunction and Outcomes in Older Adults with Chronic Kidney Disease. *Journal of the American Geriatrics Society*. 2009;57:2217-2223.
19. Demoulin N, Beguin C, Labriola L, Jadoul M. Preparing renal replacement therapy in stage 4 CKD patients referred to nephrologists: a difficult balance between futility and insufficiency. A cohort study of 386 patients followed in Brussels. *Nephrology Dialysis Transplantation*. 2011;26:220-226.
20. Pilotto A SD, Franceschi M, Aucella F, D'Ambrosio P, Scarcelli C, Ferrucci L. A multidimensional approach to the geriatric patient with chronic kidney disease. *Journal of Nephrology*. 2010;23:5-10.
21. Dalrymple L, Katz R, Kestenbaum B, et al. Chronic Kidney Disease and the Risk of End-Stage Renal Disease versus Death. *J GEN INTERN MED*. 2011;26:379-385.
22. Andrea Corsonello CP, Fabrizia Lattanzio, Sabrina Garasto, Francesco Corica, Silvia Bustacchini, Enrico E. Guffanti, Angela M. Abbatecola, Vincenzo Mari, Filippo L. Fimognari, and Raffaele Antonelli Incalzi. . Does Concealed Chronic Kidney Disease Predict Survival of Older Patients Discharged from Acute Care Hospitals? *Rejuvenation Research*. 2010;13:539-545.
23. Muntner P, Bowling CB, Gao L, et al. Age-Specific Association of Reduced Estimated Glomerular Filtration Rate and Albuminuria with All-Cause Mortality. *Clinical Journal of the American Society of Nephrology*. 2011;6:2200-2207.
24. Heras M F-RM, Sánchez R, Guerrero MT, Molina A, Rodríguez MA, Alvarez-Ude F. Elderly patients with chronic kidney disease: What happens after five years of follow-up? *Nefrologia*. 2012;32:300-305.
25. Drion I, van Hateren KJJ, Joosten H, et al. Chronic kidney disease and mortality risk among older patients with type 2 diabetes mellitus (ZODIAC-24). *Age and Ageing*. 2012;41:345-350.

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26. Marks A, Black C, Fluck N, et al. Translating chronic kidney disease epidemiology into patient care—the individual/public health risk paradox. *Nephrology Dialysis Transplantation*. 2012;27:iii65-iii72.
27. Ahmed A, Fonarow GC, Zhang Y, et al. Renin-Angiotensin Inhibition in Systolic Heart Failure and Chronic Kidney Disease. *The American Journal of Medicine*. 2012;125:399-410.
28. Binder EF, White HK, Resnick B, McClellan WM, Lei L, Ouslander JG. A Prospective Study of Outcomes of Nursing Home Residents with Chronic Kidney Disease with and without Anemia. *Journal of the American Geriatrics Society*. 2012;60:877-883.
29. Navaneethan SD, Schold JD, Arrigain S, et al. Serum triglycerides and risk for death in Stage 3 and Stage 4 chronic kidney disease. *Nephrology Dialysis Transplantation*. 2012;27:3228-3234.
30. Hemmelgarn BR, James MT, Manns BJ, et al. Rates of treated and untreated kidney failure in older vs younger adults. *JAMA*. 2012;307:2507-2515.
31. Dobre M, Brateanu A, Rashidi A, Rahman M. Electrocardiogram Abnormalities and Cardiovascular Mortality in Elderly Patients with CKD. *Clinical Journal of the American Society of Nephrology*. 2012;7:949-956.
32. Shastri S, Katz R, Rifkin DE, et al. Kidney Function and Mortality in Octogenarians: Cardiovascular Health Study All Stars. *Journal of the American Geriatrics Society*. 2012;60:1201-1207.
33. Marks A, MacLeod C, McAteer A, et al. Chronic kidney disease, a useful trigger for proactive primary care? Mortality results from a large UK cohort. *Family Practice*. 2013;30:282-289.
34. Ahmed A, Rich MW, Zile M, et al. Renin-Angiotensin Inhibition in Diastolic Heart Failure and Chronic Kidney Disease. *The American Journal of Medicine*. 2013;126:150-161.
35. Westerberg P-A, Tivesten Å, Karlsson MK, et al. Fibroblast growth factor 23, mineral metabolism and mortality among elderly men (Swedish MrOs). *BMC nephrology*. 2013;14:85-85.
36. Faller B, Beuscart J-B, Frimat L. Competing-risk analysis of death and dialysis initiation among elderly (≥ 80 years) newly referred to nephrologists: a French prospective study. *BMC Nephrology*. 2013;14:103-103.
37. Huang X, Jiménez-Moleón JJ, Lindholm B, et al. Mediterranean Diet, Kidney Function, and Mortality in Men with CKD. *Clinical Journal of the American Society of Nephrology*. 2013;8:1548-1555