# REDUCING CARDIOVASCULAR RISK IN CHRONIC KIDNEY DISEASE: A FOCUS ON MINERALOCORTICOID RECEPTOR ANTAGONIST AND ARTERIAL STIFFNESS IN PRIMARY CARE

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# ABSTRACT

Chronic kidney disease (CKD) is a major public health issue, which is associated with significant cardiovascular risk. Increased arterial stiffness is believed to be a key pathway leading to this excessive cardiovascular burden. In this thesis, the use of allopurinol, a xanthine oxidase inhibitor, was found to be associated with lower arterial stiffness amongst a cohort of high-risk, CKD patients. A systematic review and meta-analysis of the cardiovascular effects of mineralocorticoid receptor antagonists demonstrated a consistent blood pressure lowering effect but highlighted the risk of hyperkalaemia and shortage of conclusive evidence of their use on other cardiovascular outcomes in patients with CKD. A pilot randomised controlled trial was conducted aiming to examine the effect of a low-dose mineralocorticoid receptor antagonist, spironolactone, on arterial stiffness in patients with stage 3 CKD in primary care. The study was terminated early due to low recruitment rate. Qualitative studies embedded within the trial found that patients with CKD in the community were generally unaware of their diagnosis and had misconceptions and negative views on the disease terminology. Perceiving that the research topic was relevant to patients' personal health was identified as a significant prerequisite for their participation in CKD research in primary care.

# DEDICATION

To my beloved family

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# TABLE OF CONTENTS

# LIST OF FIGURES

# LIST OF TABLES

# LIST OF APPENDIX

# LIST OF ABBREVIATIONS

| | |
|---|---|
| ACEi | angiotensin-converting enzyme inhibitors |
| AGE | advanced glycation end-products |
| AIx | augmentation index |
| $AIx_{75}$ | augmentation index corrected to a heart rate of 75 beats per minute |
| ANOVA | analysis of variance |
| ARB | angiotensin II receptor blocker |
| BDI | Beck's Depression Inventory |
| BMI | body mass index |
| BP | blood pressure |
| CENTRAL | Cochrane Central Register of Controlled Trials |
| cfPWV | carotid-femoral pulse wave velocity |
| CI | confidence interval |
| CIMT | carotid intima-media thickness |
| CKD | chronic kidney disease |
| CKD-EPI | Chronic Kidney Disease Epidemiology Collaboration |
| CPRD | Clinical Practice Research Datalink |
| CrCl | creatinine clearance |
| CV | cardiovascular |
| DBP | diastolic blood pressure |
| DM | diabetes mellitus |
| DMC | data monitoring committee |
| DNA | deoxyribonucleic acid |
| DTPA | diethylene triamine pentaacetic acid |
| EDTA | ethylenediaminetetraacetic acid |
| eGFR | estimated glomerular filtration rate |
| EPR | electronic patient record |
| EQ5D-5L | European Quality of Life- 5 dimensions |
| ESRD | end-stage renal disease |
| hsCRP | high sensitivity C-reactive protein |
| HTA | Health Technology Assessment |
| IDMS | isotope derived mass spectroscopy |

| | |
|---|---|
| IEQ | Illness Effect Questionnaire |
| IgA | Immunoglobulin A |
| IPQ | Illness Perception Questionnaire |
| IPQ-R | revised Illness Perception Questionnaire |
| IPQ-B | brief Illness Perception Questionnaire |
| IPQ-MP | multi-perspective Illness Effects Questionnaire |
| IQR | inter-quartile range |
| $K^+$ | potassium ion |
| KDIGO | Kidney Disease Improving Global Outcomes |
| KDOQI | Kidney Disease Outcomes Quality Initiative |
| KDQOL | Kidney Disease Quality of Life |
| KPS | Karnofsky Performance Scale |
| LV | left ventricular |
| LVH | left ventricular hypertrophy |
| MAP | mean arterial pressure |
| MDRD | Modification of Diet in Renal Disease |
| MeSH | medical subject headings |
| mGFR | measured glomerular filtration rate |
| MHRA | Medicine and Healthcare Products Regulatory Agency |
| MR | mineralocorticoid receptor |
| MRA | mineralocorticoid receptor antagonist |
| MRC | Medical Research Council |
| $Na^+$ | sodium ion |
| NHANES | National Health and Nutrition Examination Survey |
| NHS | National Health Service |
| NICE | National Institute for Health and Care Excellence |
| NIHR | National Institute for Health Research |
| NKF | National Kidney Foundation |
| PC-CRTU | Primary Care Clinical Research and Trials Unit |
| PCT | Primary Care Trust |
| PP | pulse pressure |
| PWA | pulse wave analysis |

| | |
|---|---|
| PWV | pulse wave velocity |
| QOF | Quality and Outcomes Framework |
| QOL | quality of life |
| ROS | reactive oxygen species |
| RAAS | renin-angiotensin-aldosterone system |
| RRT | renal replacement therapy |
| RIISC | Renal Impairment in Secondary Care study |
| SAF | skin autofluorescence |
| SBP | systolic blood pressure |
| SD | standard deviation |
| SF-36 | Medical Outcomes Study Short Form 36-Item Health Survey |
| SMS | short messaging service |
| STOP-CKD | Spironolactone To Prevent Cardiovascular events in early-stage chronic Kidney Disease |
| THIN | The Health Improvement Network |
| TSC | trial steering committee |
| uACR | urine albumin:creatinine ratio |

# CHAPTER 1 INTRODUCTION

According to the latest Global Burden of Disease Study, chronic kidney disease (CKD) represents one of the top 20 leading cause of global loss of life (1). It is recognised as a growing and important public health issue, which affects up to 14% of the population of the developed world (2-5). While patients with CKD undoubtedly have heightened risk of progressing to end-stage renal disease (ESRD), their risk of cardiovascular (CV) morbidity and mortality are in fact far greater (6). Nonetheless, as patients with CKD are often asymptomatic in the early or moderate stage, the majority are unaware of their CKD diagnosis (7). In addition, there is also limited understanding regarding their illness perception and their attitudes towards CKD research participation, especially in primary care.

## 1.1 Definition of Chronic Kidney Disease

In 2001, as data from the 3rd US National Health and Nutrition Examination Survey (NHANES) highlighted the high prevalence of patients with elevated serum creatinine, it was suggested that tackling the issue with under-diagnosis and under-treatment of this particular population were crucial to curb the rising epidemic of ESRD and reduce its CV disease burden (8). However, for decades, there was a lack of a unifying term or clear definition and classification to describe the states of reduced kidney function not requiring renal replacement therapy (RRT) (9), which invariably resulted in lost opportunities for prevention (10).

Hence, in 2002, the National Kidney Foundation's (NKF) Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines proposed for the first time a working definition and five-stage classification system of CKD, irrespective of the underlying cause (11). It defined CKD as 'either kidney damage or decreased kidney function (estimated glomerular filtration rate [eGFR] < 60 ml/min/1.73m$^2$) for three or more months' (11). The kidney damage is ascertained by persistent urine albumin:creatinine ratio (uACR) of greater than 30 mg/g or abnormalities in urine sediment, blood and urine chemistry measurements, kidney biopsy or imaging results. As decreasing eGFR was known to be related to increasing prevalence of CKD associated complications, the guidelines also introduced the five-stage classification of CKD, based upon GFR levels (Table 1-1). After several minor modifications, this CKD definition and classification were later endorsed and adopted by the Kidney Disease Improving Global Outcomes (KDIGO) in 2005 and 2007 (12, 13).

Table 1-1: Kidney Dialysis Outcomes Quality Initiative (KDOQI) Guidelines and Kidney Disease Improving Global Outcomes (KDIGO): Definition and Stages of Chronic Kidney Disease (12-14).

| **Stage** | **Description** | **GFR (mL/min/1.73m$^2$)** | **KDIGO modifications** |
|---|---|---|---|
| 1 | Kidney damage with normal or increased GFR | ≥ 90 | 1-5T if kidney transplant recipient |
| 2 | Kidney damage with mild decreased GFR | 60-89 | |
| 3 | Moderate decreased GFR | 30-59 | |
| 4 | Severe decreased GFR | 15-29 | |
| 5 | Kidney failure | <15 (or dialysis) | 5D if receiving dialysis |

*Abbreviation: GFR, glomerular filtration rate*
*Note: Chronic kidney disease is defined as either kidney damage or GFR <60ml/min/1.73m$^2$ for ≥3 months. Kidney damage is defined as pathologic abnormalities or markers of damage, including abnormalities in blood or urine tests (i.e.: abnormal urine sediment or presence of urine albumin: creatinine ratio > 30 mg/g in two of three spot urine specimens) or imaging studies or presence of kidney transplant.*

By 2011, mounting evidence demonstrated the independent association between elevated albuminuria with renal, CV and survival outcomes in the meta-analyses (2, 15-17), which

prompted KDIGO to further modify the CKD classification system. It incorporated albuminuria stages, subdivided stage 3 into 3a and 3b and emphasized clinical diagnosis (18) (Table 1-2).

Table 1-2: The Kidney Disease Improving Global Outcomes (KDIGO) classification of CKD prognosis by GFR and albuminuria categories (adapted from reference) (18).

| | | | **Persistent albuminuria** | | |
|---|---|---|---|---|---|
| | | | **A1** | **A2** | **A3** |
| | | | Normal/mildly increased | Moderately increased | Severely increased |
| | | | <30 mg/g | 30-300 mg/g | >300 mg/g |
| **GFR categories** (ml/min/1.73m$^2$) | **G1** | ≥90 | Low | Moderate | High |
| | **G2** | 60-89 | Low | Moderate | High |
| | **G3a** | 45-59 | Moderate | High | Very high |
| | **G3b** | 30-44 | High | Very high | Very high |
| | **G4** | 15-29 | Very high | Very high | Very high |
| | **G5** | <15 | Very high | Very high | Very high |

*The description of low, moderate, high and very high denotes risk of progression of renal disease.

Following these landmark publications, this influential concept of CKD was widely accepted and soon led to an explosion of both clinical and research interest in this prevalent condition in the past two decades (19). Despite its critics, these clear and simple guidelines are instrumental in improving communications between physicians regarding patients with reduced kidney function, influence implementation of clinical practice guidelines and public health strategies and last but not the least, offer a vital structure for CKD research studies worldwide.

## 1.2 **Measuring and Estimating Glomerular Filtration Rate**

As excretion of waste metabolic products and achieving fluid and electrolytes balance via filtration represents the key function of kidneys, the GFR is generally considered the best overall index of kidney function (20). Accurate measurement of GFR is fundamental in establishing CKD diagnosis and guiding treatments. Direct measurement of GFR (mGFR) is achieved by assessing plasma and urinary clearance of exogenous filtration markers, for instance, inulin, iothalamate, iohexol, EDTA (ethylenediaminetetraacetic acid) or DTPA (diethylene triamine pentaacetic acid) (20, 21). However, despite being the 'gold-standard' methods, reports have shown that there were significant inter-test variations within the same measuring method as well as considerable disparities in mGFR readings amongst different methods (22). Furthermore, such techniques are often cumbersome, labour-intensive and not feasible for day-to-day practice (20), which led to the search of more accessible methods of estimating GFR using endogenous filtration markers (i.e.: creatinine, cystatin C). Interestingly, a recent observational study also suggested that mGFR was not better in predicting morbidity and mortality outcomes in CKD population compared to creatinine- or cystatin C- based eGFR (22).

Serum creatinine is mainly the metabolic product of creatine and phosphocreatine from the skeletal muscle. Since the development of Cockcroft-Gault formula to predict creatinine clearance in 1976 (23), our knowledge and understanding in estimating GFR based on the endogenous filtration markers have come a long way. Pioneered by the Modification of Diet in Renal Disease (MDRD) study group, Levey et al first published a six-variable GFR estimating equation which improved on the over-estimation of GFR associated with Cockcroft-Gault formula (24). In 2006, the MDRD eGFR formula was further simplified

into a four-variable equation, incorporating age, gender, race (African American or otherwise) and serum creatinine calibrated to an assay traceable to isotope-dilution mass spectrometry (25). Though it is not without its limitations, this equation became and remains one of the most widely used equations to calculate eGFR as it provides a reasonably accurate GFR estimation in patients with CKD. Preceded by the landmark KDOQI guidelines on the clear, multi-layered definition of the CKD based upon eGFR and coupled with the global introduction of automated reporting of eGFR (26-28), this pragmatic method of estimating GFR has drastically increased the global awareness and recognition of CKD, influenced clinical practices and public health strategies as well as transformed the landscape of CKD research.

Recently, the Chronic Kidney Disease Epidemiology Collaboration group (CKD-EPI) further advanced GFR estimation by introducing the CKD-EPI creatinine equation in 2009 (29). Though the CKD-EPI creatinine equation was reported to be more accurate than that of the MDRD in the initial publication (percentage of estimated GFR within 30% of measured GFR using CKD-EPI or MDRD equations was 84.1% and 80.6%, respectively) (29), a following systematic review found that both equation had their strengths and weakness depending on the GFR ranges (30). The CKD-EPI equation appeared to perform better at higher GFRs whilst the reverse was true for the MDRD equation (30). This improved accuracy of estimating GFR at higher range of the CKD-EPI equation has been shown to significantly reduce the prevalence of CKD and better predict the risk of ESRD and mortality, in comparison to the MDRD equation (2). These findings undoubtedly have implications in planning public health strategies and formulating epidemiology research.

In addition to serum creatinine, serum cystatin C, a cysteine proteinase inhibitor which is produced at a constant rate by nucleated cells (31), is another extensively-researched endogenous filtration marker. A meta-analysis concluded that serum cystatin C was superior to serum creatinine as a marker of GFR (32), which led to the development of two additional estimating equations based upon cystatin alone (CKD-EPI $eGFR_{cystatin\ C}$) and in combination with creatinine (CKD-EPI $eGFR_{creatinine\text{-}cystatin\ C}$) (33). The combined creatinine-cystatin C equation was shown to perform best amongst the three equations and further improved on the correct reclassification of a significant proportions of those with creatinine-based eGFR of 45-59 ml/min/1.73m$^2$ to having GFR of 60 ml/min/1.73m$^2$ or above (33).

In view of the advances made on the eGFR front in the past decade, the National Institute for Health and Care Excellence (NICE) has recently updated its guidelines on CKD, suggesting clinical laboratories to adopt the CKD-EPI equation when reporting eGFR (34). Furthermore, the guidelines also recommend physicians to consider measuring cystatin-C and using the cystatin C- based eGFR equation at initial diagnosis to rule out CKD in people with sustained creatinine-based eGFR of 45-59 ml/min/1.73m$^2$ for at least 90 days but without proteinuria or other markers of kidney disease (34).

Table 1-3: Equations used to estimate glomerular filtration rate

| | |
|---|---|
| Cockcroft-Gault estimated Creatinine Clearance equation (23) | $(140\text{-Age}) \times \text{weight} \times 0.85$ [if female] $\div (72 \times S_{cr})$ |
| 6-variable MDRD study eGFR equation (24) | $161.5 \times S_{cr}^{-0.999} \times \text{age}^{-0.176} \times 1.180$ [if black] $\times 0.762$ [if female] $\times \text{BUN}^{-0.176} \times \text{Albumin}^{+0.318}$ |
| 4-variable MDRD study eGFR equation (25) | $175 \times S_{cr}^{-1.154} \times \text{age}^{-0.203} \times 1.212$ [if black] $\times 0.742$ [if female] |
| CKD-EPI creatinine eGFR equation (29) | $141 \times \min(S_{cr}/\kappa, 1)^{\alpha} \times \max(S_{cr}/\kappa, 1)^{-1.269} \times 0.993^{\text{Age}} \times 1.018$ [if female] $\times 1.159$ [if black]<br><br>*$\kappa$ is 0.7 for females and 0.9 for males, $\alpha$ is -0.329 for females and -0.411 for males, min indicates the minimum of $S_{Cr}/k$ or 1, and max indicates the maximum of $S_{Cr}/k$ or 1.* |
| CKD-EPI cystatin C eGFR equation (33) | $133 \times \min(S_{cvs}/0.8,1)^{-0.499} \times \max(S_{cys}/0.8,1)^{-1.328} \times 0.996^{\text{Age}}$ $\times 0.932$ [if female] |
| CKD-EPI creatinine-cystatin C eGFR equation (33) | $135 \times \min(S_{cr}/\kappa, 1)^{\alpha} \times \max(S_{cr}/\kappa, 1)^{-0.601} \times \min(S_{cvs}/0.8, 1)^{-0.375} \times \max(S_{cys}/0.8, 1)^{-0.711} \times 0.995^{\text{Age}} \times 0.969$ [if female] $\times 1.08$ [if black]<br><br>*$\kappa$ is 0.7 for females and 0.9 for males, $\alpha$ is $-0.248$ for females and $-0.207$ for males, min indicates the minimum of $S_{cr}/\kappa$ or 1, and max indicates the maximum of $S_{cr}/\kappa$ or 1.* |

*Abbreviations: BUN: blood urea nitrogen; eGFR: estimated glomerular filtration rate; MDRD: modification of diet in renal disease; $S_{cr}$: serum creatinine; $S_{cvs}$: serum cystatin C*
*N/B: Age given in years, weight given in kilograms, serum creatinine and blood urea nitrogen given in mg/dL, albumin given in g/dl, creatinine levels in µmol/L can be converted to mg/dL by dividing them by 88.4.*

## 1.3 **Epidemiology of Chronic Kidney Disease**

There is significant variation in the reported estimated prevalence of CKD to date, both among and within the countries (35, 36). In the most recent U.S. Renal Data System Annual Report, the prevalence of CKD was estimated to be 13% (5). In comparison, the NEOERICA project estimated an overall prevalence of stage 3-5 CKD of 8.5% in 2007 in the United Kingdom (37), whilst a recent CKD primary care Quality and Outcomes Framework (QOF) registers 2013/14 reported an average prevalence of 4% (38). Interestingly, another UK-based epidemiological study, using two eGFRs, measured at least seven days apart, reported an even lower estimate of 3.5%, which highlighted the issues with misclassification of the diagnosis in primary care (35). Despite this variation,

studies have shown consistent increase of CKD prevalence over the years (39). Globally, while the mortality from lower respiratory infections, diarrhoeal disease, CV diseases, cancers and chronic respiratory diseases is falling, this is off-set by the rising numbers of deaths related to diabetes mellitus (DM) and CKD (1). In fact, CKD has risen from the 36$^{th}$ leading cause of global loss of life in 1990 to the 19$^{th}$ in 2013 (1).

In general, the increasing prevalence of DM, hypertension and most importantly, the ageing population are thought to be the key driving forces behind the 'CKD epidemic' (4). The prevalence of CKD increases exponentially with increasing age. While the median prevalence of CKD amongst population aged 30 years or older was estimated at 7%, the figures increased sharply to almost 36% in patients aged 64 years or older (36). Additionally, there is also a significant increase in the preponderance of older patients as the eGFR declines: the percentage of patients aged 70 years or above with eGFRs >60, 45-59, 30-44 and <30 ml/min/1.73m$^2$ was reported to be 16%, 50%, 81% and 77%, respectively, according to the data from the NEOERICA study (37). Notably, despite the incidence of CKD among 20-64 year-olds remaining stable at around 0.5% in the past few years, the raising trend of CKD incidence among those above the age of 65 years has shown no sign of abating, with a more than twofold increase between 2000 and 2008 (5).

Patients with CKD, especially those with ESRD on dialysis, are known to be associated with significant morbidity and mortality (5). However, patients with ESRD only comprise a mere 2% of the total CKD population in the U.K. (40). While the healthcare cost for each patient with ESRD is substantial, the direct and indirect healthcare needs of the large CKD population should not be under-estimated. In 2012, the U.S Renal Data System reported

Medicare expenditure of almost $45 billion for the CKD population, rising significantly from the expenditure figure of $29 billion in 2008 (5). This considerable healthcare cost of CKD represents more than 1.5 times of their total expenditure on ESRD program in the U.S. (5). In contrast, the total cost of CKD to the English NHS in 2009-2010 was estimated to be at £1.45 billion, with more than half of the budget being spent on 2% of the CKD population who require dialysis (40).

## 1.4 **Cardiovascular Disease in Chronic Kidney Disease**

Although the risk to progressing to ESRD requiring dialysis was one of the key concerns for patients with CKD, for those with early or moderate stage CKD, their competing risk of death was far greater. In fact, in a study of 3,047 patients with stage 3 CKD, the 10-year cumulative incidence of ESRD was a mere 0.04 in comparison to their mortality rate of 0.51 (6). This significant increase in mortality amongst the CKD population appeared to be heavily driven by their excessive CV burden (41). Compared with their age- and gender-matched counterparts, patients with CKD in England were found to have 7,000 excess strokes and 12,000 excess myocardial infarctions per year (40). This excess CV event alone was reported to have incurred an estimated direct healthcare cost of £174-178 million in UK in 2009-10 (40).

### 1.4.1 Chronic Kidney Disease and Cardiovascular Outcomes

Thus far, numerous large population-based longitudinal studies have consistently demonstrated the independent relationship between the presence of CKD and increased CV events (41-45). The pivotal epidemiological study by Go et al in 2004 first demonstrated the significant reversed graded association between eGFR and CV events as

well as mortality (41). After adjusting for various comorbidities, patients with eGFR 45-59, 30-44, 15-30 and <15 ml/min/1.73m$^2$ were associated with a hazard ratio for CV events of 1.4, 2.0, 2.8 and 3.4, respectively (41). The data from ARIC study also reported this independent graded increased risk of de novo atherosclerotic CV disease and recurrent atherosclerotic CV disease with each 10 ml/min/1.73m$^2$ decline of eGFR (42). Such findings were equally noted amongst those above the age of 65 years (46). Several meta-analyses have since provided confirmation on such findings (2, 16, 17). Even after adjusted for traditional CV risk factor and albuminuria, compared to those with eGFR of 95 ml/min/1.73m$^2$, patients with eGFR of 60, 45 and 15 ml/min/1.73m$^2$ had hazard ratios of all-cause mortality of 1.03, 1.38 and 3.11 (47) and hazard ratio of CV mortality of 1.11, 1.73 and 3.08, respectively, (17).

Importantly, besides being a strong risk factor, CKD is also a crucial adverse prognostic marker for those with established CV disease (48, 49). Among patients with chronic heart failure, mortality risk increased with decreasing eGFR (48). In fact, baseline renal function was found to be a stronger predictor of mortality than left ventricular (LV) ejection fraction in patients with severe heart failure (50). Likewise, such association between renal function and mortality was also noted in patients with acute coronary syndrome (51, 52), intracerebral haemorrhage (53), established vascular disease (54) and chronic stable coronary artery disease (55).

It is therefore crucial to improve our understanding of the underlying mechanisms contributing to this heightened CV burden in the CKD population and explore the potential therapeutic agents which might help in tempering the adverse CV outcomes.

### 1.4.2 Factors Contributing to Increased Cardiovascular Burden in Chronic Kidney Disease

Patients with CKD are known to have a high burden of traditional CV risk factors (41, 47). There is significantly greater prevalence of DM, hypertension, dyslipidaemia as well as prior CV disease (i.e.: coronary heart disease, stroke, peripheral arterial disease and heart failure) in the CKD population compared to the general population (41). Cross-sectional data from the NHANES showed that almost 80% of patients with CKD stages 3 to 5 CKD had two or more CV risk factors compared to 33% of those without CKD (47). Of note, the NHANES data also highlighted the suboptimal management of CV risk factors amongst CKD patients and suggested that this might have contributed to their increased CV morbidity and mortality (47). Another large U.S. cohort study of the more than 130,000 elderly participants also revealed that patients with moderate renal impairment (serum creatinine= 221-345 μmol/L) were less likely to undergo thrombolytic therapy, angiography, angioplasty or receive cardio-protective medications (i.e.: aspirin, β-blockers) during hospitalisation for myocardial infarction as compared to those with serum creatinine below 132 μmol/L (56). Nonetheless, a more recent, albeit smaller study examining the use of secondary CV prevention medications in 6,913 participants reported different findings. The use of anti-platelet agents was found to be similar across different eGFR groups (57). In fact, when compared to those with eGFR $\geq$ 60 ml/min/1.73m$^2$, patients with eGFR < 45 ml/min/1.73m$^2$ were 1.14, 1.20 and 1.10 times more likely to receive angiotensin-converting enzyme inhibitors (ACEi) or angiotensin II receptor blockers (ARB), β-blockers and statins, respectively (57).

Irrespective of the varying findings on the standard of CV risk management in CKD population, it is becoming increasingly apparent that the CV disease in CKD differs from those of the general population (58, 59). While the Framingham risk score, based upon age, gender, DM, systolic blood pressure (BP), smoking status and cholesterol profiles, is widely used to estimate individual patient risk of CV disease in the general population, it has been shown to significantly under-estimate CV events in patients with CKD at 5 and 10 years (60). This finding therefore suggested that those traditional risk factors probably have a different risk relationship with CV disease in patients with CKD compared to the general population or that there are other 'non-traditional' risk factors which are unique to the CKD which have not been accounted for (61). Some of these widely-studied, 'non-traditional' CV risk factors pertinent to the CKD population include, but not limited to, albuminuria, anaemia, mineral bone disorder, activation of the renin-angiotensin-aldosterone system (RAAS), increased oxidative stress and inflammation (58, 59, 61, 62). The high prevalence of such traditional and non-traditional risk factors is thought to contribute to the various abnormal CV phenotypes seen in the CKD population (49).

## 1.5 **Abnormal Cardiovascular Phenotypes in Chronic Kidney Disease**

The cardiac abnormalities in the CKD are typified by concentric LV hypertrophy (LVH) and LV dilatation with proportional hypertrophy (61, 63). In fact, nearly 40% of patients with CKD were found to have evidence of LVH (64). Regional, global, longitudinal or diastolic LV dysfunction as well as myocardial fibrosis were also some of the other features of cardiomyopathy associated with CKD (63). Notably, many of these cardiac and vascular abnormalities are evident even in patients with early CKD (65, 66) despite satisfactory blood pressure (BP) control (67). Indeed, a study of 40 patients with early or

moderate stage CKD clearly demonstrated subclinical abnormalities of LV myocardial deformation on detailed cardiac magnetic resonance imaging, despite apparently preserved conventional echocardiographic measures of systolic function (68).

With regards to vascular abnormalities, there are two distinct but overlapping pathological phenotypes associated with CKD: atherosclerosis and arteriosclerosis (69). Atherosclerosis is primarily an intimal disease characterised by patchy distribution of fibro-atheromatous plaques, leading to vascular occlusion. In contrast, arteriosclerosis is a diffuse disease of the arterial medial layer associated with increased collagen content, vascular calcification, hypertrophy and hyperplasia of vascular smooth muscle cells, resulting in thickening and hardening of the arteries (58). Accelerated atherosclerosis is common among patients with CKD leading to the increased prevalence of coronary artery disease, stroke and peripheral arterial disease (61). Though such vasculo-occlusive events remain one of the important causes of death among the CKD population, a greater proportion of CV deaths in CKD are in fact attributable to sudden cardiac death, arrhythmia and congestive heart failure (5). Hence, other pathological changes, for instance, arteriosclerosis, endothelial dysfunction and cardiomyopathy are therefore thought to play an essential role in contributing to the heightened CV events in patients with CKD (61).

Elastic arteries are important to buffer the pressure oscillations resulting from the intermittent ventricular ejection (70). They provide a ‘cushioning function’ to supply steady blood flow to peripheral organs and tissues (70). During systole, the stroke volume generated by the LV is partially forwarded to the peripheral tissues (71). The elasticity of the proximal aorta allows part of the systolic pressure generated by the heart to be

transformed into elastic force and the distended vessel accommodates the rest of the stroke volume (71). During diastole, the recoiled aorta will then propelled these 'reserved' volume of blood forward to facilitate continuous blood flow to the peripheral tissues (71). As the artery compliance decreases, the energy requires to expand the artery increases. Hence, reduction or loss of arterial distensibility does not only augment arterial systolic and pulse pressure, increase arterial circumferential stress, but it also exposes the myocardial, cerebral and renal microvasculature to excessive fluctuations in flow and pressure (72).

In the general population, increasing arterial stiffness has long been known to be associated with advancing age (73). This age-related arterial stiffening is coupled with increased ventricular systolic stiffness even in the absence of hypertrophy (74). Such premature ageing or stiffening of the aorta was well-documented amongst patients with ESRD (75, 76). However, these changes are not solely confined to those with advanced CKD. Mourad et al first described the positive correlation between creatinine clearance (CrCl) and carotid compliance after adjustment for age, gender and BP (65). Subsequently, others had further demonstrated a stepwise increase in arterial stiffness with the declining CrCl, eGFR and advancing CKD stages (77-79). In a multivariate analysis of 95 patients with mild to moderate CKD, Briet et al also highlighted the independent relationship between GFR and arterial stiffness (80). Though several recent studies did not find such consistent, direct correlation between levels of arterial stiffness and severity of CKD (81-83), most agreed that overall, CKD population is associated with increased arterial stiffness compared to their counterparts. Importantly, Edwards et al observed that the reduction of aortic distensibility and increment of ventricular systolic and diastolic

stiffness, resembling those of heart failure with preserved ejection fraction, occurred as early as stage 2 CKD (67). This characteristic cardiac remodelling in CKD was postulated to be part of the mechanisms in maintaining the arterial-ventricular coupling and cardiac performance in the presence of ever increasing afterload pressure related to arterial stiffness (67). Thus, the prevalent increase of arterial stiffness in the CKD population is believed to be a key, early mechanistic pathway that leads to LV hypertrophy, myocardial fibrosis, systolic as well as diastolic cardiac dysfunction and culminating in excessive CV morbidity and mortality (58).

### 1.5.1 Measurements of Arterial Stiffness

Devices such as Complior (Alam Medical, Vincennes, France), Sphygmocor (AtCor Medical, Sydney, Australia), PulsePen (Diatechne, Milan, Italy), PulseTrace (Micromedical, Chatham Maritime, UK), Arteriograph (TensioMed Kft., Budapest, Hungary) and Vicorder (Skidmore Medical, Bristol, UK) allow simple and direct measurement of pulse wave velocity (PWV) (84), which facilitate studying arterial stiffness in various high CV risk populations.

Proposed by Bramwell and Hill in 1922 (85), the propagative model of the circulatory system illustrated that the velocity of pulse wave correlates inversely with the distensibility of the artery (85, 86). Since then, others have also highlighted the important influence of reflected waves on aortic pressure wave forms (87-89). As there is a gradual reduction of arterial elasticity, from proximal to distal, along the arterial tree, this unique feature therefore enables the generation of wave reflection to amplify the propagating pressure

wave, resulting in the 'amplification phenomenon', whereby the peripheral pressure wave becomes greater that than of central's (86).

Based upon these concepts, PWV represents a non-invasive, most widely-used, validated and the gold-standard method of arterial stiffness measurement (84, 90). Other available methods to calculate arterial stiffness also include using vascular echotracking techniques, magnetic resonance imaging or applanation tonometry to calculate pressure-diameter relationship or indirectly estimate arterial stiffness via diastolic pressure decay modelling or aortic characteristic impedance (84). Though it can be measured at various sites, carotid-femoral PWV (cfPWV), which corresponds to aortic stiffness, is of the most clinical relevance amongst all as it has been demonstrated to be an independent predictor of adverse CV outcomes in a wide range of populations (86). For both studies detailed in this thesis (RIISC and STOP-CKD), the Vicorder was the device used for measuring cfPWV (see section 4.3.5.2)

### 1.5.2 Implications of Increased Arterial Stiffness

Arterial stiffness as measured by cfPWV has significant prognostic value across different populations. It has been shown to be an independent determinant of CV events, CV mortality and all-cause mortality in the general and elderly population (91-96) as well as in patients with hypertension (97-100), DM or glucose intolerance (101), CKD (102) and ESRD (103-106). In fact, in several studies, arterial stiffness demonstrated stronger prognostic value than other traditional risk factors, including systolic BP (SBP) (92, 94, 101). A meta-analysis of 17 longitudinal studies, including diverse populations, concluded that each 1 m/s increase of arterial stiffness measured by cfPWV, correlated to an increase

adjusted risk of approximately 15% in total CV events, CV mortality or all-cause mortality (107). Interestingly, this predictive ability of arterial stiffness in total CV events and CV mortality was found to be significantly greater amongst patients with higher baselines CV risk, including the ESRD population, as compared to the general population (107).

However, the data on the predictive value of arterial stiffness in progression to ESRD amongst the CKD population is conflicting. While Taal et al and Ford et al demonstrated an independent association between arterial stiffness and the rate of renal function decline or progression to ESRD (108-110), others did not (111, 112).

### 1.5.3 Therapeutic Approaches to Reduce Arterial Stiffness

Over the years, numerous mechanisms of increased arterial stiffness in CKD have been postulated. In addition to the effect of ageing and increased prevalence of traditional CV risk factors, other reasons which were believed to contribute to alteration of extracellular matrix or endothelial dysfunction and hence resulted in acceleration of arteriosclerosis in CKD population includes formation of advanced glycation end-products (AGE) (113), activation of RAAS (114, 115), increased oxidative stress (116), vascular calcification (117, 118) and chronic inflammation (58). Although the mechanisms leading to arterial stiffening in CKD appear to be multifactorial, complex and most likely inter-linked, identification of some of these key pathways may provide opportunities to develop therapeutic targets in attenuating this unfavourable vascular remodelling.

In the general population, aerobic-endurance exercise (119-121), low salt diet (122), moderate alcohol consumption (123, 124), consumption of n-3 fatty acid (125) or

isoflavones (126) as well as increased dietary intake of phytoestrogen (127) had been implicated in improving arterial compliance. Thus far, with regards to the pharmacological approaches, antihypertensive agents including ACEi, ARB, calcium channel blockers and mineralocorticoid receptor antagonists (MRAs) as well as AGE cross-links breakers such as aminoguanidine, have shown promising effects on arterial stiffness reduction in various populations (128).

Nonetheless, research data on such approaches focusing on the CKD population remain scarce. Two small-scale studies involving patients with ESRD suggested that sevelamer, a non-calcium-based phosphate binder which lowers gastro-intestinal phosphate absorption, improves, or at least attenuates the progression aortic stiffness (129, 130). Another study of 21 patients with secondary hyperparathyroidism on dialysis demonstrated reduction of cfPWV after 12 months of cinacalcet treatment (131). However, a study of 120 non-diabetic patients with stage 3 CKD did not provide evidence that sevelamer carbonate improves LV mass, LV function or arterial stiffness (132). With regards to the effect of statins on arterial stiffness, a double-blinded study involving 37 patients with serum creatinine levels > 120 μmol/L reported that atorvastatin prevented the progression of aortic stiffening when compared with placebo (133). Though a systematic review published in 2010 showed conflicting results in regards to the effect of statins on arterial stiffness, several recent studies in hypertensive patients demonstrated consistent beneficial effects as those seen in the CKD cohort (134-136).

Amongst all of the antihypertensive agents, the effect on arterial stiffness reduction by RAAS pathway inhibitors appeared to be independent of BP (137, 138). The use of ACEi

was associated with LV mass reduction (139) and favourable survival in patients with ESRD (138). A double-blinded, placebo-controlled study has also explored the use of low-dose spironolactone (a non-selective MRA) in patients with stage 2-3 CKD (140). Encouragingly, patients receiving spironolactone were found to have significant improvements in arterial stiffness and LV mass after 40 weeks of treatment (140).

This thesis aims to examine the potential effect of two pharmacological agents: xanthine oxidase inhibitor and MRA, on arterial stiffness. Further discussions of the possible mechanisms by which these two pharmacological agents affect CV surrogate markers and CV outcomes are detailed in section 1.7.

## 1.6 **Cardiovascular Risk Management in Chronic Kidney Disease**

Despite the heightened CV risk in patients with CKD, there is often a lack of information to guide management (141), and over-reliance on *post-hoc* or subgroup analyses of studies in the general population, which might be prone to bias (142). Applying treatment strategies verified in the general population to patients with CKD is a highly debatable approach for several reasons, including the unique CV pathophysiology and risk profile as discussed (143). This issue with the paucity of evidence is epitomised by the uncertainty in BP management, which is considered the core of the CV management in CKD. Thus far, though observational studies have established that elevated BP is associated with increased risk of renal disease progression (144-146), the optimal BP range for patients with CKD remains less certain, especially for those with minimal albuminuria (147, 148).

Two decades ago, the MDRD study demonstrated that a tighter mean arterial pressure (MAP) slowed the renal progression in CKD population with proteinuria > 1g/ day (149). Likewise, although intensive BP control showed no benefit on renal progression in the overall cohort of AASK study, it hinted at a probable beneficial effect amongst those with the baseline proteinuria > 220 mg/g (150). Together with the observation studies, these trials therefore formed the basis of the several nephrology guidelines, recommending a tighter BP target of <130/80 mmHg for the CKD population with proteinuria, until the present (151-153). Nonetheless, on closer inspection, the conclusion from both the RCTs was in fact drawn from a subgroup analysis, as the overall intention-to-treat analysis of the RCT revealed no significant benefit between the groups. Even within the subgroup analysis of the MDRD study, the benefit seen with intensive BP control was solely driven by the 54 patients with proteinuria > 3g/day at baseline (151). A recent systematic review of 11 RCTs concluded that although intensive BP control did appear to reduce the risk of renal progression and ESRD, it was only amongst those with proteinuria (147). Such strategies in fact failed to demonstrate any convincing, beneficial effect on CV events or mortality. Additionally, there were substantial variations regarding the definition of 'intensive BP-lowering strategies' across the included studies (i.e.: MAP < 92 mmHg, BP <120/80 mmHg, diastolic BP [DBP] < 75 mmHg, etc.), which made implementing such conclusions to practice particularly tricky (147). This is further complicated by the finding of a J-shape relationship between SBP and poorer outcomes in CKD population, as several studies have observed the significant increased stroke risk, CV or all-cause mortality amongst those with SBP < 120 mmHg compared to their counterparts (154-156).

While the optimal BP target to reduce CV burden for patients with CKD remains a debatable issue, there is growing consensus on the beneficial role of RAAS blockade in CKD, which appeared to be independent of its effects on BP and albuminuria reductions (152, 153). Aside from being a regulator of fluid and electrolytes balance and a potent mediator of BP via arterial vasoconstriction, RAAS have also been implicated in its role in the up-regulation of chronic inflammation and fibrosis (157, 158). A patient-level meta-analysis published in 2003 reported that the use of ACEi was associated with better renal outcomes even after adjustment for BP and urine protein excretion in CKD population (153). Though, another similar meta-analysis published 2 years after appeared to be less convinced of their benefit on kidney disease progression (159), a more recent pooled analysis by Balamuthusamy et al revealed that in comparison with placebo, RAAS blockade reduced risk of myocardial infarction, heart failure and total CV outcomes in CKD patients (160).

With regards to the use of statins, the most recent meta-analysis concluded that statin therapy reduces CV morbidity and mortality as well as all-cause mortality in patients with all stages of CKD, though the observed beneficial effects appear to be less among patients with advanced CKD or ESRD (161).

Thus far, the only evidence-based pharmacological agents available in attenuating adverse outcomes in CKD population therefore appeared to be limited to BP control, especially using RAAS blockade, and lowering LDL-cholesterol with statin-based therapy. With this backdrop, NICE recently updated its guidelines on early identification and management of CKD in primary and secondary care in 2014. In terms of CV management, it recommends

a tight BP target of 130/80 mmHg or less for those with DM or uACR > 70 mg/mmol, but a BP target of <140/90 mmHg, in parallel with the general population, for the non-diabetic, CKD population without significant albuminuria. In addition, the guidelines also encourage the use of ACEi or ARB. Though it suggests the use of low-dose statins for primary and secondary CV prevention, there is no specific guidance regarding the assessment of their CV risk and the threshold of starting statin treatment primary prevention remains unclear. As in line with the non-CKD population, the guidelines suggest offering antiplatelet medications to patients with CKD for secondary prevention of CV disease, but highlight the associated increased risk of bleeding (34).

### 1.6.1 Quality and Outcomes Framework in Chronic Kidney Disease Management

In response to the high prevalence of CKD and its significant association with increased morbidity and mortality, the Department of Health first introduced CKD as part of the Quality and Outcomes Framework (QOF) in 2006. The QOF is essentially an 'annual reward and incentive programme detailing general practice achievement results', intended to benefit both patients and the National Health Service (NHS) (162). It measures practice achievement against a wide range of 'evidence-based' clinical indicators. The CKD domain of QOF from 2006 till 2015 included five clinical indicators (see Table 1-3). Since its introduction, the UK observed an drastic reduction of incidence of 'late-presenters', defined as patients with progression of CKD entering services as acute emergencies, from 31% to 19% in the past few years (163).

Table 1-4: The Quality and Outcomes Framework (QOF) domain 2014/15 in Chronic Kidney Disease

| **Indicator** | **Points** | **Achievement threshold** |
|---|---|---|
| Records | | |
| CKD001. The contractor establishes and maintains a register of patients age 18 or over with CKD (US National Kidney Foundation: Stage 3 to 5 CKD) | 6 | |
| Ongoing management | | |
| CKD002. The percentage of patients on the CKD register in whom the last blood pressure reading (measured in the preceding 12 months) is 140/85 mmHg or less | 11 | 41-81% |
| CKD003. The percentage of patients on the CKD register with hypertension and proteinuria who are currently treated with an ACEi or ARB | 9 | 45-80% |
| CKD004. The percentage of patients on the CKD register whose notes have a record of a urine albumin:creatinine ratio (or protein:creatinine ratio) test in the preceding 12 months | 6 | 45-80% |

Nonetheless, the latter three indicators (CKD002, CKD003, CKD004) have since been removed from the 2015/16 QOF document (164). According to the General Practitioners (GP) Committee and executive lead on QOF, such drastic changes were intended to reduce the focus on box-ticking and enable GPs to treat patients according to their clinical needs (165). This decision also perhaps reflected the quandary highlighted by Fink et al that despite clear evidence showing the association between CKD and poor outcomes, fervent desire by all parties (i.e.: policy makers, healthcare professionals, patients, etc.) to improve the outcomes, there is astonishingly little good-quality, compelling evidence to make strong recommendations in guiding the management of such heterogeneous groups of patients (166).

### 1.6.2 Quality and Quantity of Research Evidence in Chronic Kidney Disease

Indeed, a previous editor of two prestigious medical journals expressively conveyed his concerns regarding the decline of basic research in nephrology several years ago (167). In

addition, the deficiencies of translational research were also thought to be contributing to the majority of the day-to-day practical dilemmas encountered in nephrology (168).

Due to their well-documented advantages, randomised controlled trials (RCTs) represent the gold standard for testing hypotheses in medical research (169, 170). Nonetheless, renal medicine has a poor track record for producing good quality, large-scale RCTs. In an evaluation of the number and quality of RCTs, nephrology was found to have published fewer than 12 other medical specialties (169). The proportion of all nephrology citations that were RCTs was only 1%. Another analysis of the journal citations from 1998 to 2010, disappointingly echoed similar findings (171). Among nine sub-specialities of internal medicine, nephrology journals remained to have the lowest impact factor (171). Indeed, a recent authoritative and comprehensive systematic review looking at studies right up to November 2011, struggled to find large, high quality RCTs from which to make strong recommendations on screening and monitoring early stage CKD (166). In particular, they found that evidence of outcomes in CKD patients was scant and often derived from *post hoc* analyses of subgroups of patients enrolled in trials. Few trials reported or systematically collected information about adverse events suggesting the possibility of selective reporting and publication bias (166).

Strippoli et al first highlighted the pervasive issues of unclear allocation concealment, lack of blinding of outcome assessors and failure to perform intention-to-treat-analysis in RCT reporting in nephrology more than a decade ago (169). A recent study by Deo et al regrettably continued to report similar findings (172). Disappointingly, more than a quarter of the RCTs were found to have failed to describe their primary outcome and the majority

were criticised to be poor in handling and reporting data lost to analysis (172). Studies in patients with CKD in the past have often produced negative or neutral results, which might be attributable to several pivotal methodological flaws (173). The issues with missing primary outcome designation and conflicting results amongst RCTs in nephrology may be in part, fuelled by the lack of consensus regarding the various definition of renal-endpoints (i.e.: doubling of creatinine, decline of eGFR > 25%, requiring dialysis, etc) as well as over-reliance of its use in short-term studies (174). Often, the studies were also underpowered as a consequence of 'over-optimistic' assumptions about event rates and the impact of therapeutic interventions. These factors clearly need to be taken into account when planning future trials as information gleaned from good quality, rigorously conducted pilot studies is essential when designing large, adequately powered hard-endpoint studies (175).

## 1.7 **Potential Pharmacological Agents for Cardiovascular Intervention**

Several potential therapeutic agents aiming at reducing traditional or non-traditional risk factors have been under research for CV intervention in CKD. This thesis will be focusing on two of these therapeutic agents: (1) Xanthine oxidase inhibitor and (2) MRA.

### 1.7.1 Xanthine Oxidase Inhibitors

Uric acid is the oxidation end-product of purine metabolism. Renal elimination of uric acid accounts for the majority (75%) of its disposal, whilst the rest was via gastro-intestinal route (176). Uric acid has been shown to have positive association with several inflammatory markers (177), stimulate the inflammatory pathway (178), impair nitric oxide generation (179), promote vascular smooth muscle cells proliferation and upregulate

the pro-thrombotic effects mediated by platelet activation (180), all of which contribute to the pathogenesis of hypertension, endothelial dysfunction and hence, vascular disease and stiffening. There is an abundance of data showing the association between hyperuricaemia and increased arterial stiffness (181, 182), CV events and mortality in the general population, even in physiological range (183-191). A recently published study using Mendelian Randomisation further strengthened the evidence of the causal relationship between hyperuricaemia and adverse CV outcomes, especially sudden cardiac death (192). Additionally, raised uric acid level has also been found to be an independent risk factor for developing CKD in a meta-analysis containing more than 190,000 participants (193).

Hyperuricaemia is highly prevalent in the CKD population (194). In a study of 223 patients with Immunoglobulin A (IgA) nephropathy, hyperuricaemia was independently associated with progression of kidney disease, defined by increment of creatinine > 20 % (195). In the post-hoc analysis of MDRD study, hyperuricaemia was also reported as an independent risk factor for both CV and all-cause mortality in patients with stage 3-4 CKD (196). Nonetheless, despite accumulating evidence demonstrating associations between hyperuricaemia with adverse outcomes, a recent meta-analysis demonstrated no association between changes in serum uric acid level and risk of CV events or all-cause mortality (197).

While the role of elevated uric acid level simply as a risk marker rather than a modifiable CV risk factor remains contentious, studies exploring the use of the xanthine oxidase inhibitors (i.e.: allopurinol and febuxostat) in reducing vascular dysfunction have yielded encouraging results (198-201). Xanthine oxidase inhibitors are uric acid lowering agents

widely used as treatments for chronic gout. They inhibit the formation of uric acid from xanthine and hypoxanthine reducing serum uric acid levels and preventing crystallization. . In addition to their uric acid lowering effect, importantly, xanthine oxidase inhibitors have long been shown to have direct free radical scavenging action (202). Indeed, the mechanism through which allopurinol improved endothelial function was thought not to be related to uric acid lowering, but to its ability to reduce vascular oxidative stress in patients with chronic heart failure (203). Xanthine oxidase is one of the enzymatic systems involves in the production of reactive oxygen species (ROS) (204). Over-production of ROS, which exceeds the defence mechanisms of anti-oxidants, is believed to result in oxidation of essential biological macromolecules (i.e.: deoxyribonucleic acid [DNA], protein, membranes, etc.). Additionally, as superoxide radicals readily inactivate endothelial NO, thereby impairing vaso-relaxation, there is an accumulating body of evidence demonstrating that oxidative stress contributes significantly to endothelial dysfunction in cardiovascular disease (205), which conceivably contributes to increased arterial stiffness and CV disease (58, 204). . In animal models, xanthine oxidase inhibitors were found to reduce vascular free radical production (206, 207), improve blood pressure and endothelial function (208-210) as well as prevent hypertension-induced left ventricular and renal hypertrophy (211, 212). Among patients with CKD, the use of allopurinol has thus far been demonstrated to be associated with improvements in surrogate markers for CV disease including endothelial function (198, 199) and LVH (198). Furthermore, in an RCT of 113 patients with eGFR < 60 ml/min/1.73m$^2$, the use of allopurinol has also been found to be associated with improved inflammatory markers, reduced hospitalisations, and significantly lower risk of CV events over the 2-year follow-up period (200, 201).

Nonetheless, the potential beneficial effect of allopurinol in retarding renal disease progression is not clear. Limited by substantial heterogeneity of baselines characteristics across the eight included studies, a meta-analysis published in 2014 was unable to make clear conclusion regarding the effect of allopurinol on renal outcomes in patients with CKD (213). Interestingly, a post-hoc data analysis of an RCT by Goicoechea et al demonstrated not only persistent favourable outcomes on CV events, but also on renal progression amongst the group originally assigned with allopurinol treatment, despite significant number of treatment cross-overs during the five additional years of follow-up (200).

Although these results are encouraging, the general consensus is that a blanket clinical use of xanthine oxidase inhibitors in patients with CKD based on the existing body of evidence is still very premature. In our striving towards reducing the disease burden in the CKD population, xanthine oxidase inhibitors warrant further investigation.

### 1.7.2 Mineralocorticoid Receptor Antagonists

Aldosterone is a mineralocorticoid which is one of the key effectors of the RAAS. Traditionally, it is known for its function on kidneys and colon epithelium in regulating $Na^+$ reabsorption and $K^+$ secretion, which forms part of the feedback loop in RAAS and BP control (214) (Figure 1-3). This classic action of aldosterone is dependent on the transcription and translation of the genes, resulting in the synthesis of protein stimulating transport, and is therefore termed the ‘genomic’ action.

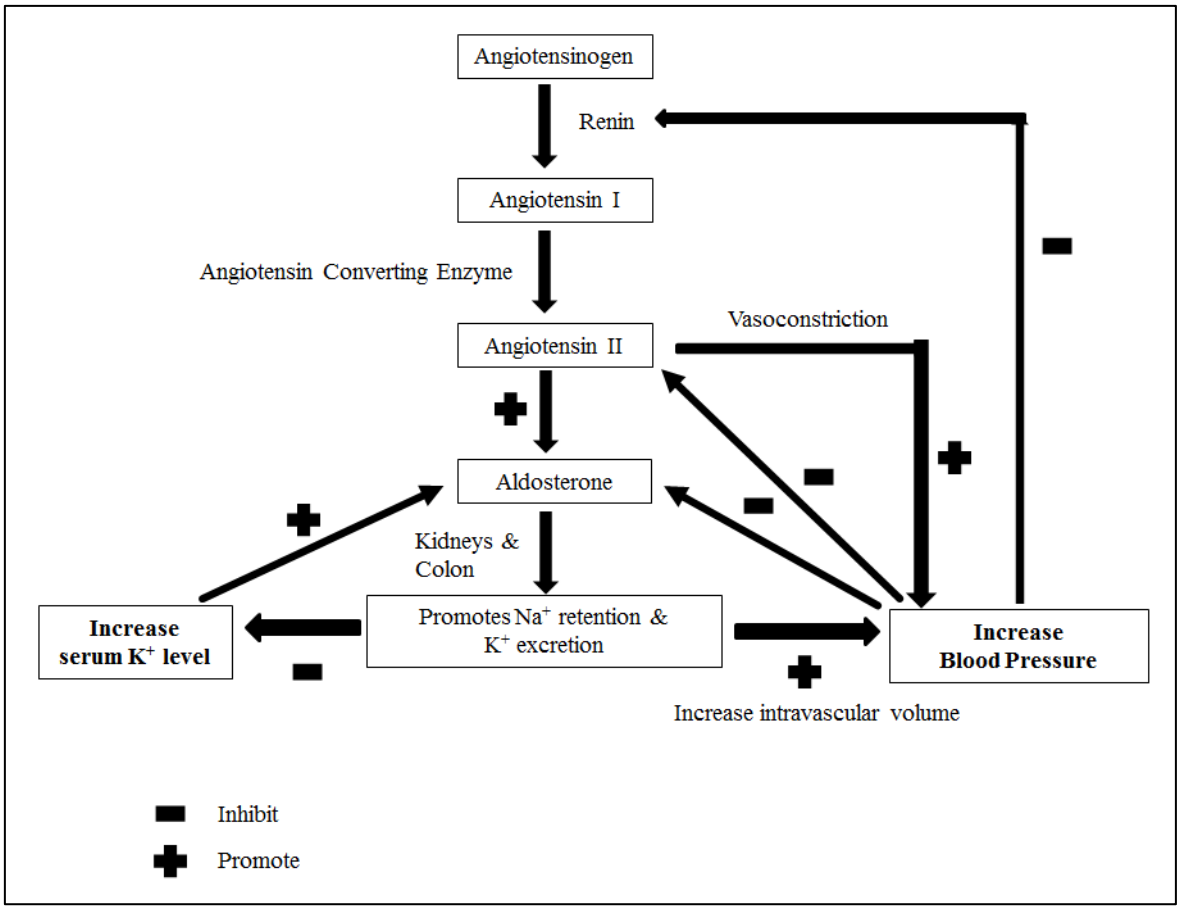



Figure 1-1: Genomic actions of aldosterone and its associated feedback loops.

Beyond these classical actions of aldosterone, there has been growing interest and shift of focus onto its wider arrays of non-genomic effects in the recent years (215). Unlike the genomic actions which have a latent period of 30-60 minutes, the non-genomic actions of aldosterone were rapid (latency < 15 minutes) and not solely confined to kidneys or colon (216). Extensive expression of mineralocorticoid receptors has been identified in the heart, endothelial cells, vascular smooth muscle cells as well as in kidney mesangial cells. These non-genomic actions of aldosterone have therefore gained particular interest in the field of cardiology and are believed to be a crucial mediator in pathological remodelling of both the CV and renal systems (214, 217).

Thus far, there is a substantial body of evidence demonstrating the role of aldosterone in numerous CV effects, including endothelial dysfunction, transmural arterial inflammation and ultimately, myocardial and vascular hypertrophy and fibrosis/stiffening independent of BP control (218-221). *In vitro*, aldosterone was reported to enhance epidermal growth factor receptor, (222), stimulate collagen abundance in human aortic smooth muscle cell in the presence of reactive oxygen species (223), induce osteopontin gene expression of the endothelial cells (224), up-regulate chemoattractant proteins and facilitate the transmigration of monocytes to the sub-endothelium (225, 226), all of which are implicated in vascular dysfunction and invariably leads to increase arterial stiffening Experimental research in animal models also demonstrated its role in promoting oxidative stress, inflammation, sclerotic and fibrotic changes in both the kidneys and CV systems (217). Furthermore, Di Zhang et al reported cross-talk between angiotensin II and aldosterone signalling in cardiac remodelling, hence concluded that their effects on CV system are additive (218). In human beings, a high aldosterone level was associated with higher LV mass, increased arterial stiffness, endothelial dysfunction and insulin resistance (227). Many of these deleterious effects of aldosterone were also found to be independent of BP or angiotensin II actions (217). Use of MRAs, which inhibits the action of aldosterone, appears to attenuate these detrimental effects (217).

Thus far, the RAAS remains a principal target for CV intervention, and inhibitors of this system (ACEis or ARBs) have been used widely in improving hypertension and proteinuria in patients with CKD (228-230). Nonetheless, the effect of RAAS blockade is not always efficient in normalising BP, proteinuria and CV risk. In fact, in a certain subset of patients, prolonged use of ACEIs and ARBs, regardless of dose and class (231-233), can

lead to ‘aldosterone breakthrough’(234). Though it is a well-recognised phenomenon, there is no clear consensus on the definition of ‘aldosterone breakthrough’. While it is generally regarded as elevation of post-treatment plasma aldosterone level from pre-treatment baseline (235), some non-CKD studies defined it as aldosterone level above the normal range, which varies considerably across different laboratories and studies (231, 232, 236, 237).

Amongst patients with diabetic or IgA nephropathy, the incidence of aldosterone ‘breakthrough’ is high and reported to be 28-53% (233, 238-240). Nonetheless, the current evidence regarding the clinical significance of the presence of ‘aldosterone breakthrough’ is conflicting, which is likely to be related to short study duration and methodological limitations (234). While some investigators have reported an association between ‘aldosterone breakthrough’ with greater proteinuria (233, 238), others have not (239, 240). Similarly, while Schjoedt et al demonstrated association between ‘aldosterone breakthrough’ with renal progression in a small study of type 1 diabetic nephropathy (239), this finding was, however, not evident in a larger post-hoc analysis of a RCT (240). Nonetheless, amongst those with ‘aldosterone breakthrough’, Sato et al demonstrated that the use of low dose spironolactone significantly reduced albuminuria and LV mass index without change in BP after 24 weeks (238).

Thus far, the beneficial CV effect of aldosterone blockade, in addition to standard treatment, is perhaps best evidenced by the heart failure studies. In the RALES and EPHESUS studies, that use of MRAs was proven to confer significant reduction in morbidity and mortality among patients with heart failure (241, 242). These landmark

findings were later confirmed in a meta-analysis (243). With regard to the CKD population, in addition to its role in reducing proteinuria (244-247), other studies have also suggested improvement of multiple surrogate markers of CV disease with the use of MRAs (247). Nevertheless, its role in long-term CV outcomes in patients with CKD remains uncertain.

In a randomised, double-blinded, placebo-controlled trial of 112 patients with stage 2 or 3 CKD in the secondary care setting, Edwards *et al.* demonstrated that the addition of a MRA, spironolactone, 25 mg once daily to background ACEi or ARB treatment safely reduced LV mass ($-14 \pm 13$ g versus $+3 \pm 11$ g, $p < 0.01$) and decreased arterial stiffness (cfPWV: $-0.8 \pm 1.0$ m/s versus $-0.1 \pm 0.9$ m/s, $p < 0.01$), compared with placebo (140, 248, 249). A trial to examine whether these desirable intermediate endpoints changes can be translated into long-term gains in terms of reduced CV morbidity and mortality in large CKD cohort is clearly warranted.

## 1.8 **Qualitative Research in Chronic Kidney Disease**

Although there is an increasing number of a quantitative research study exploring the effects of various pharmacological interventions in improving CKD outcomes, issues regarding patients' illness experience and disease perceptions on CKD, especially in the early or moderate stage remain under-researched.

In the NICE CKD 2014 guidelines, it was emphasized that patients with CKD should be informed of their diagnosis, involved in shared decision making and supported in self-management (34). Nevertheless, a large recent UK study highlighted the issue of poor

awareness among patients with stage 3 CKD, whereby a staggering 41% of them were unaware of their CKD diagnosis (7). As the majority of the patients often remain asymptomatic especially in the early or moderate stage, the combination of CKD being a silent condition and the issue of low diagnosis awareness among patients undoubtedly creates barriers in treatment delivery and potentially affects patients' outcomes. Hence, there is a clear need for further research into early and moderate stage CKD to examine the issues underlying low CKD illness awareness, explore patients' illness perceptions, identify patients' perceived knowledge gap and improve understanding of the needs amongst this large, growing, distinct group of patients. In addition, this in-depth understanding of patients' perceptions of CKD will also form the foundation for exploring the barriers to their participation in research studies. Such knowledge is not only paramount in informing future healthcare resource planning, but is also crucial in formulating future research questions and study design in CKD.

## 1.9 **Illness Perceptions of Patients with Chronic Kidney Disease**

In the past few decades, there have been a growing number of studies assessing illness experience and quality of life (QOL) in patients with kidney disease. Questionnaires or scoring systems, for example, Beck's Depression Inventory (BDI), Medical Outcomes Study Short Form 36-Item Health Survey (SF-36), Kidney Disease Quality of Life (KDQOL) instrument and Karnofsky Performance Scale (KPS) have been used to quantify symptoms or disease burden. Much research has been focusing on patients with ESRD, whereby issues with depression, anxiety and sexual dysfunction are prevalent (250-253) and QOL is known to be markedly lower than the general population (254). Though the disease burden is generally less in patients with early or moderate stage CKD, its

significant negative impact on patients' physical and mental QOL is nonetheless noticeable even in its early stages (255). This implies that in addition to disease burden, other factors clearly are in play affecting patients' QOL and outcomes. Above all, patients' perception of illness is believed to be one such crucial factors. Illness perception thus far has been shown to influence patients' illness behaviour, coping strategies, psychosocial well-being and QOL in various chronic illnesses, including patients with ESRD (256-260).

This awareness of the importance of the psychological aspects of the illness experience is clearly not novel. Engel's call for an integrated biopsychosocial model which incorporated social, psychological and behavioural dimensions of illness to replace the biomedical model almost four decades ago, revolutionised the approach in understanding, researching and managing various diseases (261). The psychosocial reaction to illness was referred to 'a set of cognitive, emotional and behavioural responses induced by every sick person by all the illness-related information they received' (262).

### 1.9.1 Theoretical Models of Illness Perceptions

Aiming to promote a more balanced scientific and humanistic approach towards patients' care and ensuring physicians were equipped with the skills to deal with the patients' psychological aspects, Lipowski formulated a theoretical framework proposing the four domains of 'meaning of illness' (challenge or threat, loss, gain or relief and punishment) and four main categories of 'determinant of meaning' (intrapersonal factor, interpersonal factor, illness-related factor as well as sociocultural and economic factors) (263).

Recently, increasing attention has been paid to exploring a more dynamic model of illness representation and health behaviours (264). Illness representations are patients' beliefs and expectations about an illness or somatic symptom. First proposed in 1980, Leventhal et al conceptualised patients' common-sense representations of health and illness via a self-regulatory framework (260). This common-sense theoretical model of self-regulation enables the organisation of the multitude of information required when evaluating a certain health behaviour as well as incorporating coping actions and appraisal (265). Initially based upon a simple Fear-Drive reduction model (266), Leventhal et al assumed that fear (health threat) motivated actions or procedures to eliminate or reduce fear (health threat) and that these actions or procedures were then reinforced or learnt (267). However, the lack of interaction between fear levels and action plans in the initial health behavioural studies led to the development of the parallel process model. The parallel process model postulated that health threat generates cognitive as well as emotional representations of threat, both of which trigger parallel corresponding actions to manage the perceived threat (danger control) and emotional fear (fear control) (267). Building further upon the model, Leventhal et al theorised that patients act as common-sense scientists when constructing representations of health threat and categorised the knowledge of the health threat into five domains: identity, timeline, consequences, cause and control (268) (Figure 1-4). The meanings of each domain are detailed in Table 1-4 and each domains contain both abstract (semantic) and concrete (perceptual or experiential) information with a bi-directional link between the two (268). In addition, Cameron et al also theorised the rule of 'symmetry' which refers to the pressure to connect or anchor the abstract with the concrete and vice versa (268). With each addition and integration of new information, the illness

representation modulates, evolves and develops both in the cognitive and emotional sense in order to response to the change.

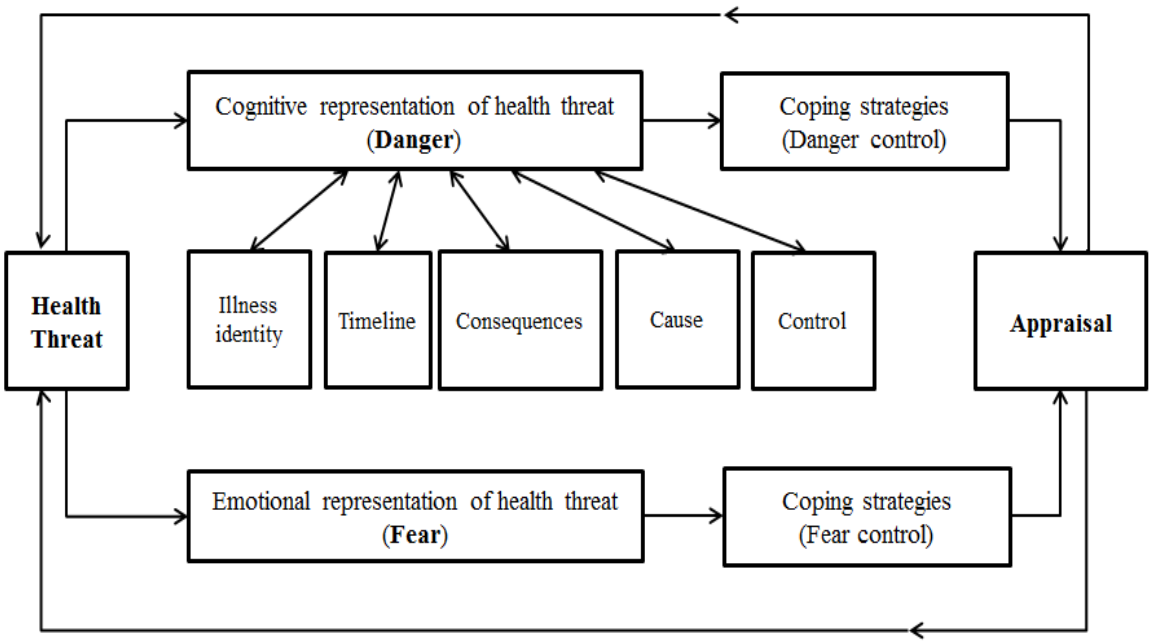



Figure 1-2: The common-sense self-regulatory model of illness and health behaviour. Adapted from Cameron et al 2002 (268).

Table 1-5: Five dimensions of illness representation and examples of abstract and concrete information in each dimensions (268).

| | Meaning | Abstract ⟷ Concrete | |
|---|---|---|---|
| **Identity** | Label placed on the disease and the symptoms associated with it | My blood pressure is high. | My legs are swollen. |
| **Timeline** | Perceived duration/course of illness | This cough will last for a few weeks. | It seems this cough has lasted as long as this house. |
| **Consequences** | Beliefs about the severity of the illness and its expected outcomes or impacts on life functions | This kidney problem will shorten my life. | My kidney failed and I ended up on dialysis a year ago. |

| | | | |
|---|---|---|---|
| **Cause** | Personal ideas about the cause(s) of the illness | This illness is caused by a flu virus. | My cousin passed on this nasty flu to me. |
| **Control** | Perceived management of the illness. Beliefs about the extent to which the disease is amenable to control or cure | This chemotherapy is going to stop the cancer from spreading. | The doctor showed me that my cancer has reduced by 2cm in size since I started with this medication. |

#### *1.9.1.1 Quantitative Studies of Illness Perception in Kidney Disease*

This illness representation framework later formed the basis of the Illness Perception Questionnaire (IPQ), revised Illness Perception Questionnaire (IPQ-R), brief Illness Perception Questionnaire (IPQ-B) and multi-perspective Illness Effects Questionnaire (IPQ-MP), all of which aim to quantify patients' illness perception and have been used in various chronic medical conditions (259). Another widely used questionnaire is the Illness Effect Questionnaire (IEQ) developed by Greenberg and Peterson (269).

To date, much research has utilised such questionnaires to quantitatively study illness perception in patients with ESRD. Amongst patients on maintenance haemodialysis, lower consequence perceptions were reported to predict non-adherence of fluid intake (270) while negative emotional perceptions and unawareness of the chronicity of the illness was associated with poorer diet and medication self-care behaviours (271). Importantly, Covic et al also found that patients' QOL score was not associated with dialysis treatment duration, but with their illness perceptions (272). The study reported that personal control and time-line component of illness perceptions correlated positively, while emotional response correlated negatively with the QOL (272). Similarly, Fowler et al also described the negative correlation between index of well-being with perceived consequences and emotional response (273).

The majority of these studies have demonstrated patients' illness perception as a powerful tool in influencing coping mechanisms and predicting both psychological and clinical outcomes in patients with ESRD (274-278). Importantly, a recent systematic review of patients with ESRD summarised the association between negative perception of illness with increased mortality (259). Patients' apparent interpretation of their illness is therefore as, if not more, crucial in predicting patients' outcomes than co-morbidities or disease characteristics (277). However, its potential role as a modifiable prognostic factor is yet to be fully studied and utilised.

Compared to the dialysis population, illness perception among the pre-dialysis CKD population remains an under-researched subject. Though patients on dialysis were found to perceive more illness consequences and consider that their treatment controls their illness more strongly than CKD patients in the pre-dialysis phase (279), perceived autonomy and self-esteem levels among patients with stage 4 CKD were nonetheless strongly influenced by their illness and treatment perceptions (280). Likewise, in another study of patients with stage 3b to stage 5 CKD, including those with ESRD, illness perceptions were shown to significantly influence the occurrence of anxiety or depression (281).

#### *1.9.1.2 Qualitative Studies of Illness Perception in Kidney Disease*

Though the use of a questionnaire to assess illness perception among patients with advanced CKD has been widely implemented, a study evaluating the validity of the IPQ-R in patients with different stages of CKD suggested that the questionnaire should be interpreted with care in earlier stages of CKD or if few symptoms are reported (264). In

addition, it highlighted the need to capture uncertainty regarding illness identity in this particular group of patients (264).

An interview study conducted in Taiwanese patients with early stage CKD identified six emergent themes, which included experiencing early symptoms, self-interpreting the causes of having CKD, realising CKD is a long-term disease, believing CKD could be controlled by following doctors' orders, anticipating the consequences of having CKD, and adopting coping strategies to delay the progress of CKD (282). In contrast, CKD was perceived to be a silent, treacherous and terminal disease among patients participating in a preventive renal programme in Colombia (283). Patients in early stages of CKD often described fear of the need for dialysis or transplantation and were aware of the irreversible and serious nature of their condition (283). Interestingly, despite these concerns, these patients remained stoic and felt that they were able to continue to live ‘a normal life’ as they understood that the early stages of CKD are often asymptomatic (283). Using a modified version of Lipowski’s ‘meaning of illness’ schema, a mixed-method research examining CKD patients with or without dialysis and renal transplant recipients treated at a Northern England Renal Unit noted that most patients regarded their illness as a ‘challenge’ in life that they could overcome or had to endure (284). The study categorised their meaning of illness into eight categories- challenge, value, enemy, punishment, strategy, weakness, relief and irreparable loss (284). Intriguingly, a lesser proportion of patients with CKD not requiring dialysis were noted to select ‘value’ and a greater proportion selected ‘loss’ as compared to those on dialysis or renal transplant recipients (284). Illness perceived as ‘value’ implied a view that “the experience will make one a stronger person” while illness perceived as ‘loss’ signified a view that “one’s disease is

getting worse or may die or lose the ability to function as before". The main concerns of patients with CKD not requiring dialysis were found to be related to their prognosis or to their perceived lack of improvement (284). These apparent differences in views among patients with different stages of CKD identified in both quantitative and qualitative studies clearly warrant further exploration.

An Australian focus group study of patients with all stages of CKD described the influence of healthcare service experience on patient's illness perception and highlighted the issue with inadequate information, psychosocial and practical support (285). Another exploratory Canadian study of patients with mild to moderate CKD similarly reported searching for evidence, realising kidney disease is forever, managing the illness, self-caring and the need for disease-specific information as the key themes (286). Though the findings from these studies may not necessarily be generalisable to the NHS experience, they do provide insights into the role that healthcare information plays in empowering patients with early stages of CKD.

To date, though several research studies have been conducted to quantitatively and qualitatively evaluate this issue, the majority of these studies focused mainly on patients with advanced CKD receiving dialysis (287-289). Even when early or moderate stage CKD patients were included in the studies, their viewpoints were often combined with those with ESRD, risking overlooking or diluting their specific perspectives and needs (284, 285). Though the disease burden is undoubtedly much greater and the healthcare resource is considerably more intensive for each patient with ESRD, the overall impact of the much more prevalent early or moderate stage CKD should not be underestimated and

clearly requires further research. Crucially, as only one of the studies was conducted in the UK (284), the differences in culture and healthcare systems across the studies conducted in various countries meant that the findings might not be applicable or relevant to the UK CKD population. Additionally, despite the prevalence of CKD, research studies are often plagued by poor research participant recruitment. It is plausible that patients' views on CKD related research and their willingness to participate in the studies are influence by their illness perceptions. There is therefore a pressing need for qualitative research to further explore CKD illness perceptions amongst patients with early to moderate stage CKD in the UK.

## 1.10 **Patients' Perception on Research in Chronic Kidney Disease**

While 82% of the public believes it is important for the NHS to offer opportunities to participate in healthcare research according to a recent national poll in the UK, the majority of research studies continue to be mired by poor recruitment (290). In fact, a review of 114 multi-centre cohort trials funded by the UK Medical Research Council (MRC) or the Health Technology Assessment (HTA) Programme revealed that two in three trials failed to achieve their original sample sizes and half required an extension for the study due to poor recruitment rate (291). In addition to having significant impact on the timelines and financial resources of the studies, poor recruitment of research participants can also severely jeopardise the power and validity of the study, leading to false negative outcomes, or even resulting in early termination (292). In fact, in another recent study which examined nearly 7,000 CV studies registered on the registry of ClinicalTrial.gov over a period of 13 years, almost 11% of the studies were found to have terminated prematurely (293). Of these early-terminated trials, an astonishing 54% were primarily

attributed to low recruitment (293). There was therefore a general consensus to focus on increasing value and reducing waste in research in recent years (294-300).

A review by the Cochrane Collaboration examined the effect of various strategies to improve recruitment to RCTs (301). Telephone reminders to non-responders; use of opt-out, rather than opt-in procedures for contacting potential trial participants; and open designs appeared to be effective in increasing recruitment. However, the lack of blinding as a significant trade-off in open designs needs to be considered carefully as it undoubtedly increases risk of bias (301). Furthermore, financial incentives and short messaging service (SMS) message to potential participants also appear promising and warrant further evaluation while evidence for several other interventions, including use of video and certain types of change to consent procedure was otherwise inconclusive (301). The review therefore highlighted the clear need for further research into effective strategies in optimising recruitment in view of the current gap of knowledge. Indeed, an initiative entitled 'trial forge' was recently set up in order to improve the evidence base for trial decision making and increase trial efficiency (302).

Patients' opinions are invaluable in formulating the optimal strategies to improve recruitment, which is pertinent and applicable to individual study aims and designs. In brief, understanding patients' perception, engaging patients in research design, identifying barriers to recruitment, exploring ways to overcome barriers are therefore paramount in facilitating research recruitment, with an ultimate aim for improving the quantity as well as the quality of the research evidence to guide CKD management.

## 1.11 Summary and Scope of Thesis

CKD is a significant public health issue, which is associated with high CV risk and incurring substantial costs to the healthcare system. However, there is a disconcertingly lack of good quality research evidence in guiding the management of these patients. In addition, there also appears to be a misplaced focus of research activities in the secondary care while the majority of CKD patients are in fact managed in primary care by their GPs. Hence, there is a clear need to establish feasibility of conducting large-scale RCTs in CKD in primary care and identify barriers to such research participation, which are invaluable in facilitating future research designs.

To date, several potential therapeutic options for modulating CV risk in CKD are on the horizon. Amongst them, xanthine oxidase inhibitors and MRAs have shown promising preliminary outcomes in studies thus far. Further research is clearly warranted to assess their use.

Nonetheless, despite the medical advances in the diagnosis and management of patients with CKD in the past few decades, there are growing concerns regarding the low illness awareness amongst patients with early to moderate CKD in the community. Furthermore, there is also limited understanding regarding their illness perceptions and willingness to CKD research participation, which is fundamental to provide guidance for future CKD research and reduce barriers in research recruitment.

This thesis therefore consists of four broad aims:

1. Explore the relationship between the use of allopurinol and arterial stiffness in CKD population in a cross-sectional study in secondary care;
2. Systematically review the CV effects of MRAs in CKD in published literature;
3. Examine the CV effect of low-dose spironolactone in CKD in primary care via a pilot RCT and ascertain the feasibility of such RCT in CKD in the primary care;
4. Qualitatively study patients' perception of CKD in primary care and explore the barriers to patients' research participation in CKD study.

## 1.12 **Structure of Thesis**

This thesis began with an introduction which outlined the definition and epidemiology of CKD, CV disease burden in CKD, issues of lack of research evidence in guiding the management of CV risk in CKD and highlighted the two potential agents for CV intervention in CKD, i.e.: xanthine oxidase inhibitors and MRAs. The introduction also emphasized the need to incorporate qualitative studies to enrich the research evidence, described the data regarding illness awareness as well as illness perceptions in CKD and underlined the importance of gathering further qualitative information on patients' perceptions on research participation in primary care in CKD. This will be followed by Chapter 2 which describes the methods and results of a cross-sectional study conducted to examine the association between the use allopurinol and arterial stiffness in CKD. Chapters 3, 4 and 5 focus on the CV effects of MRAs in CKD population. The methods and results of a systematic review and meta-analysis summarising the CV effects of MRAs is presented in Chapter 3 while Chapter 4 details the methodology of a feasibility RCT which aimed to examine the effect of low-dose spironolactone on arterial stiffness in CKD in primary care (The STOP-CKD study). Chapter 5 reports the quantitative outcomes of

the STOP-CKD study and describes the research recruitment issues encountered by the trial. As a mixed-method trial, the STOP-CKD study incorporated a qualitative interview component, which examined patients' perceptions of CKD and explored the barriers to CKD research participation in primary care setting. The results from this qualitative study fed back into the issues highlighted by the RCT and are presented and discussed in Chapters 6 and 7. Lastly, the main findings of thesis are summarised and concluded in Chapter 8.

# CHAPTER 2 ASSOCIATION OF ALLOPURINOL WITH ARTERIAL STIFFNESS REDUCTION IN CHRONIC KIDNEY DISEASE

## 2.1 Introduction

Asymptomatic hyperuricaemia is associated with increased CV and all-cause mortality in the general population (183-188) and in patients with CKD (194-196, 303-305). Hyperuricaemia is highly prevalent among CKD population (194). Thus far, the use of the xanthine oxidase inhibitor, allopurinol in patients with CKD have been shown to improve surrogate markers for CV disease including endothelial function (198, 199) and LVH (198). In addition, a single-blinded RCT of 113 patients with CKD has also demonstrated that allopurinol use was associated with a slower progression of renal dysfunction and a reduction in CV events (200, 201, 306).

Arterial stiffness is thought to be a key initiating factor contributing to the elevated CV risk observed in patients with CKD (58). Carotid-femoral PWV is considered to be the current 'gold-standard' measurement of arterial stiffness (86). Although allopurinol has been shown to improve endothelial function, lower central aortic pressure and regress LVH in patients with CKD, its effects on cfPWV remain unclear (198). We therefore, examined the relationship between allopurinol use and cfPWV in patients with CKD recruited into the Renal Impairment In Secondary Care (RIISC) cohort study (307).

## 2.2 **Subjects and Methods**

### 2.2.1 Ethics Statement

The study was approved by the South Birmingham Local Research Ethics committee (reference: 10/H1207/6) and all participants gave informed and written consent. The study was conducted in accordance with the Declaration of Helsinki. (Clinical Trials Registration Number: NCT01722383; Date of Registration: November 11, 2012).

### 2.2.2 Study Design and Participants

The RIISC study is a prospective, observational cohort study of patients with CKD with evidence of, or at high risk of, renal disease progression. The inclusion and exclusion criteria have previously been reported in detail (307). In brief, patients were included if they had stage 3 CKD with a declining MDRD eGFR of ≥5 ml/min/year or ≥10 ml/min/5years or a uACR ≥70 mg/mmol on three consecutive occasions, or stage 4 or 5 CKD. GFR was estimated using the four-variable MDRD equation with serum creatinine recalibrated to be traceable to an isotope derived mass spectroscopy (IDMS) method (24). Patients with established renal failure receiving dialysis treatment and patients receiving immunosuppressive medication were excluded from the study. From October 2010 to November 2012, 437 out-patients under regular follow-up were recruited from renal clinics at two large teaching hospitals in the United Kingdom.

### 2.2.3 Baseline Measurements

Baseline clinical information on participants' demographics, renal diagnosis, diagnosis of DM, CV history, past medication history, family history, concomitant medication,

smoking and alcohol consumption history were recorded. Presence of CV disease was defined by history or other evidence of angina, previous myocardial infarction, previous stroke or transient ischaemic attack, peripheral vascular disease, a previous revascularisation procedure or heart failure. Presence of DM was defined as receiving treatment for DM or a confirmed clinical diagnosis of diet-controlled DM. Smoking history and pack years were determined by participant self-reporting. An allopurinol user was defined as a participant who was receiving any dosage of allopurinol on recruitment. We contacted the GPs of all allopurinol users to obtain further details on the reason for prescription, presence of side effect related to allopurinol in the initial three months of treatment and start date of allopurinol to determine the duration of exposure.

Peripheral BP was measured in the dominant arm using a British Hypertension Society approved automated oscillometric sphygmomanometer (BPM-100, BpTRU$^{TM}$), which obtained a series of six BP readings at 1-minute intervals after 5 minutes of rest (308). Mean BpTRU BP was derived from the average of the 2$^{nd}$ to 6$^{th}$ BP readings. Carotid-femoral PWV was measured non-invasively using the Vicorder system (Skidmore Medical, Bristol, UK) as previously described by Pucci et al (309). This is an operator independent and highly reproducible technique with low within-subject variation (309). After 5 minutes of lying supine, cfPWV measurements were obtained in duplicate; the mean of two measurements was used in data analyses. Central pressure waveforms were derived and analysed using PWA as previously described (310). The central pressure waveform was analysed to determine the augmentation index (AIx) and central aortic pressures. AIx represents the difference between the second and first peaks of the central pressure waveform in systole, expressed as a percentage of the pulse pressure. Given the

known effects of heart rate, AIx was corrected to a heart rate of 75 beats per minute ($AIx_{75}$) (311).

Routine laboratory testing included blood haematological (Beckman Coulter Haematology Analyzer) and biochemical profiles as well as uACR (Roche Hitachi 702 Analyser). Additional samples were centrifuged and serum was aliquoted and stored at $-80^0$C and subsequently batch analysed for high sensitivity C-reactive protein (hsCRP) using a commercially available assay (SpaPlus assay, Binding Site). Tissue AGE level was determined by skin autofluorescence (SAF) using a validated AGE Reader$^{TM}$ (DiagnOptics BV, Groningen, The Netherlands).

### 2.3 **Statistical Analysis**

Statistical analysis was performed using SPSS version 19.0 (SPSS Inc, Chicago, IL). Numerical values were expressed as mean (standard deviation [SD]) for parametric data or median (interquartile range [IQR]) for non-parametric data. Normality of the distribution of data was assessed by visual inspection of histogram and normal probability plot (312). Non-parametric variables were log transformed prior to analysis to achieve normal distribution. If normal distribution was not achieved after transformation, non-parametric tests were used. Parametric continuous data were compared using student t-tests and non-parametric using Mann-Whitney tests. Pearson or Spearman's bivariate correlation analysis was used to examine the relationship between parametric and non-parametric numerical variables, respectively. Correlation coefficient factors were expressed as 'r' for Pearson correlation analyses and 'rho' for Spearman's analysis. Categorical data were compared by $\chi^2$ tests. As age correlated strongly with arterial stiffness, we divided the

studied population into four age quartiles. Two-way analysis of variance (ANOVA) was performed to examine the interaction between age and the use of allopurinol as well as their individual effect on cfPWV. In addition, multiple linear regression was performed to explore the relationship between cfPWV and independent variables. Missing data was excluded by cases pairwise during analyses. Statistical significance was defined as a two-tailed p value $<0.05$.

## 2.4 **Results**

### 2.4.1 Baseline Characteristics

Four hundred and thirty-seven patients were recruited of whom 14 did not have cfPWV measured for technical reasons and were therefore excluded from the study. One patient who was receiving febuxostat, an alternative xanthine oxidase inhibitor, was also excluded. In total, 422 patients were included in the analyses. The numbers of individuals at each stage of study are detailed in Figure 2-1. The baseline demographic and biochemical characteristics of the study population are shown in Table 2-1. The mean age was 63 (SD: 16) years with 60% of male gender and 71% of white ethnicity. Use of antihypertensive agents was common and 67% were receiving either an ACEi or ARB. A small number (5%) were on both an ACEi and an ARB. There was a high prevalence of hyperuricaemia; 84% had a serum uric acid concentration greater than 360 μmol/L. The frequencies of different stages of CKD were: stage 1, 0.2%; stage 2, 1%; stage 3a, 5.3%; stage 3b, 23.1%; stage 4, 61.7%; stage 5, 8.7%. Seventy-seven patients (18%) were receiving regular allopurinol, 61% as a dose of 100 mg/day (range: 50-400 mg/day). Haemodynamic parameters are presented in Table 2-2.

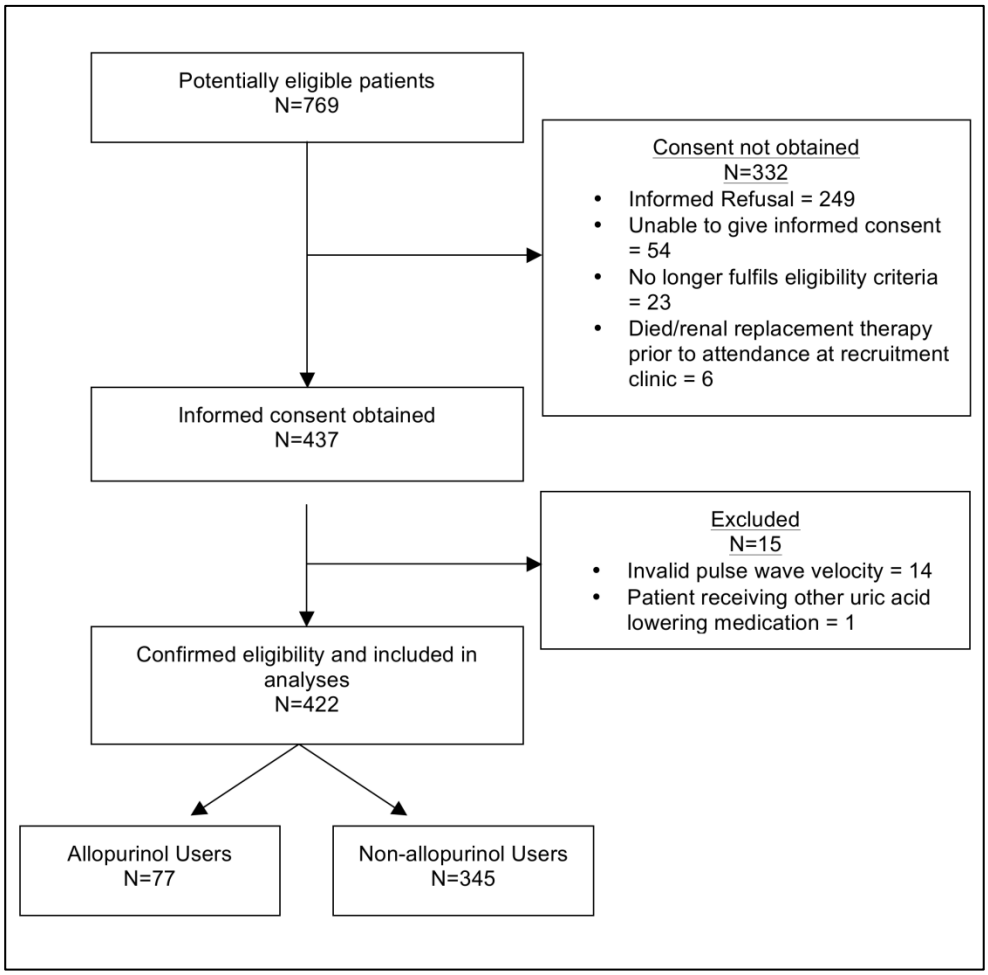



Figure 2-1: Flow chart of participants included in the study

Table 2-1: Baseline demographic, clinical and biochemical characteristics of all participants and according to the usage of allopurinol.

| | **All participants (n= 422)** | **Allopurinol user (n=77)** | **Non-allopurinol user (n=345)** | **P Value** | Number missing data (%) |
|---|---|---|---|---|---|
| Age (years) | 63 ± 16 | 62 ± 15 | 64 ± 17 | 0.31 | 0 |
| Male | 225 (60%) | 59 (77%) | 196 (57%) | **0.001** | 0 |
| Ethnicity | | | | **0.006** | 1 (0.2) |
| White | 301 (71%) | 67 (87%) | 234 (67%) | | |
| Asian | 64 (15%) | 4 (5%) | 60 (17%) | | |
| Afro-Caribbean | 40 (10%) | 3 (4%) | 37 (11%) | | |
| Body Mass Index (kg/m$^2$) | 29.8 ± 6.8 | 31.8 ± 6.4 | 29.3 ± 6.8 | **0.003** | 9 (2) |
| Presence of Diabetes Mellitus | 152 (36%) | 24 (31%) | 128 (37%) | 0.33 | 0 |
| Presence of CVD | 142 (34%) | 21 (27%) | 121 (35%) | 0.19 | 0 |
| Current smoker | 58(14%) | 4 (5%) | 54 (16%) | **0.02** | 0 |
| Ex-smoker | 174 (41%) | 35 (46%) | 139 (40%) | 0.41 | 0 |
| Smoking pack years *§§ | 2 (0-22) | 0 (0-15) | 2 (0-24) | 0.25 | 13 (3) |
| Number of antihypertensive agents | 2.4 ± 1.3 | 2.5 ± 1.0 | 2.4 ± 1.4 | 0.49 | 6 (1) |
| Use of ACEI/ARB | 281 (67%) | 55 (71%) | 227 (66%) | 0.32 | 0 |
| Use of thiazide | 24 (6%) | 1 (1%) | 23 (7%) | 0.10 | 0 |
| Use of Antiplatelet agents | 166 (39%) | 37 (48%) | 129 (37%) | 0.08 | 0 |
| Use of Statin | 247 (59%) | 46 (60%) | 201 (58%) | 0.81 | 0 |
| Duration of allopurinol exposure (months) | - | 74 ± 54 | - | - | 18 (23) |
| Serum creatinine*§ (µmol/L) | 213 (169-263) | 216 (174-270) | 212 (167-263) | 0.77 | 6 (1) |
| eGFR*§ ( ml/min/1.73m$^2$) | 25 (19-31) | 26 (21-33) | 24 (19-31) | 0.24 | 6 (1) |
| Urine ACR*§ (mg/mmol) | 35.0 (6.9-163.1) | 40.1 (7.4-134.3) | 33.8 (6.7- 166.7) | 0.70 | 45 (11) |
| Serum uric acid (µmol/L) | 479 ± 121 | 431 ± 123 | 489 ± 117 | **<0.001** | 8 (2) |
| Cholesterol (mmol/L) | 4.6 ± 1.2 | 4.5 ± 1.1 | 4.7 ± 1.2 | 0.33 | 5 (1) |
| Corrected calcium (mmol/L) | 2.26 ± 0.14 | 2.25 ± 0.14 | 2.26 ± 0.14 | 0.82 | 10 (2) |
| Phosphate*§ (mmol/L) | 1.13 (0.99-1.28) | 1.10 (1.00-1.23) | 1.13 (0.98-1.30) | 0.50 | 7 (1) |
| hsCRP*§ (mg/L) | 3.280 (1.228-9.332) | 3.678 (1.215-9.246) | 3.203 (1.257-9.332) | 0.92 | 103 (24) |
| SAF (a.u.) | 3.0 ± 0.8 | 2.8 ± 0.7 | 3.1 ± 0.8 | **0.02** | 60 (14) |

*Data are presented as frequency (percentage), mean ± standard deviation or *median (interquartile range).*
*Parametric data was analysed using unpaired two-tailed t-test or Pearson's $\chi^2$unless otherwise specified.*
*§Log-transformed prior to analyses. §§Analysed using Mann-Whiteney U test*
*Abbreviations: ACR= albumin creatinine ratio; bpm= beats per minutes; CVD= cardiovascular disease; ACEI= angiotensin converting enzyme inhibitor; ARB=Angiotensin II receptor blocker; eGFR= estimate glomerular filtration rate, hsCRP= high sensitivity C-reactive protein; SAF= skin autofluorescence.*

Table 2-2: Haemodynamic parameters of all participants and according to the usage of allopurinol.

| | All participants (n= 422) | Allopurinol user (n=77) | Non-allopurinol user (n=345) | P Value | Number missing data (%) |
|---|---|---|---|---|---|
| Peripheral SBP (mmHg) | 129 ± 20 | 126 ± 22 | 129 ± 20 | 0.19 | 14 (3) |
| Peripheral DBP (mmHg) | 76 ± 13 | 76 ± 12 | 75 ± 13 | 0.59 | 14(3) |
| Peripheral PP (mmHg) | 71 ± 18 | 67 ± 18 | 72 ± 17 | **0.02** | 16 (4) |
| Central SBP (mmHg) | 141 ± 20 | 136 ± 22 | 142 ± 20 | **0.02** | 16 (4) |
| Central PP (mmHg) | 65 ± 18 | 61 ± 18 | 66 ± 17 | **0.02** | 16 (4) |
| AIx (%) | 21 ± 9 | 20 ± 9 | 21 ± 9 | 0.45 | 12 (3) |
| $AIx_{75}$ (%) | 21 ± 9 | 20 ± 8 | 21 ± 9 | 0.35 | 12 (3) |
| Heart Rate (bpm) | 69 ± 13 | 68 ± 15 | 69 ± 15 | 0.42 | 8 (2) |
| cfPWV (m/s) | 10.2 ± 2.4 | 9.5 ± 2.3 | 10.3 ± 2.4 | **0.006** | 0 |

*Abbreviations: AIx: augmentation index; $AIx_{75}$= augmentation index adjusted to heart rate of 75bpm; bpm= beats per minute; DBP= diastolic blood pressure; SBP= systolic blood pressure; PP= pulse pressure; cfPWV= carotid-femoral pulse wave velocity*

### 2.4.2 Use of Allopurinol

The demographic, clinical and biochemical characteristics of the cohort and a comparison between allopurinol users and non-allopurinol users is shown in Table 2-1. There was significantly higher proportion of patients of male gender and white ethnicity and a significantly lower proportion of patients who were current smokers among allopurinol users. Allopurinol users had a higher body mass index (BMI) than non-allopurinol users. There was otherwise no significant difference in age, prevalence of DM, prevalence of CV disease, percentage of ex-smokers, smoking pack years, total number of antihypertensive agents used and use of ACEi or ARB between the groups. Allopurinol users had significantly lower serum uric acid concentrations and lower SAF level compared to non-allopurinol users. Other biochemical variables, including kidney function, albuminuria, lipid and bone profiles and hsCRP levels were not different between the groups. Allopurinol users had significantly lower peripheral and central pulse pressures (PP), central SBP and cfPWV (Table 2). There were no differences in heart rate, peripheral SBP, AIx and $AIx_{75}$ between allopurinol and non-allopurinol users.

Among the 77 allopurinol users, details regarding allopurinol prescription were available from their primary care physician on 59 patients. Ninety four percent were commenced on allopurinol for gout and 6% for asymptomatic hyperuricaemia. Side effects were reported in 12% during the first 3 months of allopurinol treatment: 3 had acute gout, 2 had a skin rash, 1 had diarrhoea and 1 complained of increased thirst. The mean duration of allopurinol use at recruitment was 74 months (SD: 54 months).

### 2.4.3 Use of Allopurinol and Pulse Wave Velocity

Univariate correlations with cfPWV are shown in Table 2-3. Although BMI positively correlated with serum uric acid level ($r=0.178$, $p<0.001$), there was no significant correlation between BMI and cfPWV. Uric acid levels, kidney function and hsCRP also did not correlate with cfPWV. In participants who were not receiving ACEi or ARB (n=141), there was no correlation between uric acid and cfPWV ($p=0.66$). Six percent of participants were receiving a thiazide. Use of thiazide did not correlate with levels of uric acid ($p=0.58$) or cfPWV ($p=0.66$).

Pulse wave velocity positively correlated with increasing age, white ethnicity, SAF, peripheral and central SBP and PP. Ex-smokers and smoking pack years had a significant positive correlation with cfPWV whilst current smoking did not. Use of allopurinol (mean difference: -0.8 m/s; 95% confidence interval [CI], -0.2 to -1.4 m/s, $p=0.006$), use of ACEi/ARB and Afro-Caribbean ethnicity were also associated with lower cfPWV. Neither the dose of allopurinol or duration of use of allopurinol had a significant correlation with cfPWV. Fifty-one percent (n=39) of the allopurinol users had a uric acid level below 416

μmol/L. Among allopurinol users, there was no difference in cfPWV between those with a uric acid below or above this threshold (p=0.92).

Table 2-3: Univariate analyses with carotid-femoral pulse wave velocity as the dependent outcome variable.

| | Correlation coefficient | P value |
|---|---|---|
| **Demographics** | | |
| Age (years) | 0.534 | **<0.001** |
| Gender (Male) | 0.088 | 0.07 |
| Ethnicity | | |
| White | 0.105 | **0.03** |
| Asian | 0.014 | 0.77 |
| Afro-Caribbean | -0.105 | **0.03** |
| Body Mass Index (kg/m$^2$) | -0.057 | 0.25 |
| Presence of diabetes mellitus | 0.082 | 0.09 |
| Presence of cardiovascular disease | 0.044 | 0.37 |
| Current smoker | 0.021 | 0.67 |
| Ex-smoker | 0.198 | **<0.001** |
| Smoking Pack Years** | 0.244 | **<0.001** |
| | | |
| **Haemodynamics** | | |
| BpTRU Peripheral SBP (mmHg) | 0.320 | **<0.001** |
| BpTRU Peripheral DBP (mmHg) | -0.061 | 0.21 |
| Peripheral PP (mmHg) | 0.454 | **<0.001** |
| Central SBP (mmHg) | 0.440 | **<0.001** |
| Central PP (mmHg) | 0.442 | **<0.001** |
| AIx (%) | 0.024 | 0.63 |
| $AIx_{75}$ (%) | 0.023 | 0.64 |
| | | |
| **Biochemical markers** | | |
| Serum creatinine* (μmol/L) | 0.039 | 0.43 |
| eGFR ( ml/min/1.73m$^2$)* | -0.078 | 0.11 |
| Urine ACR (mg/mmol)* | -0.042 | 0.40 |
| Serum uric acid (μmol/L) | -0.035 | 0.48 |
| Cholesterol (mmol/L) | -0.080 | 0.11 |
| Corrected calcium (mmol/L) | -0.001 | 0.98 |
| Phosphate (mmol/L)* | 0.019 | 0.71 |
| hsCRP (mg/L)* | 0.062 | 0.27 |
| SAF (a.u.) | 0.253 | **<0.001** |
| | | |
| **Medications** | | |
| Use of allopurinol | -0.135 | **0.006** |
| Dose of allopurinol (mg) | -0.185 | 0.11 |
| Duration of allopurinol exposure (months) | -0.019 | 0.89 |
| Use of ACEI/ARB | -0.163 | **0.001** |
| Use of thiazide | 0.021 | 0.66 |

*Abbreviations: ACEI= angiotensin converting enzyme inhibitor; ACR= albumin creatinine ratio; AIx: augmentation index; $AIx_{75}$= augmentation index adjusted to heart rate of 75bpm; ARB= angiotensin II receptor blocker; SBP= systolic blood pressure; DBP= diastolic blood pressure; PP= pulse pressure; SAF= skin autofluorescence.*
*Parametric data was analysed using Pearson correlation unless otherwise specified.*
**Natural Log transformed prior to analyses.*
***Non-parametric data was analysed using Spearman's bivariate correlation analysis.*

Two-way ANOVA was used to explore the impact of age and use of allopurinol on cfPWV. Participants were divided into quartiles of age (19-50, 51-65, 66-76 and 77-92 years). Pulse wave velocity increased with age and was significantly lower in non-allopurinol users (Figure 2-2). There was no interaction between age and use of allopurinol ($p=0.27$). There were significant main effects for both age and use of allopurinol, with age having a large effect size (partial eta squared=0.201, $p<0.001$) and use of allopurinol having a small albeit significant effect size (partial eta squared=0.011, $p=0.03$).

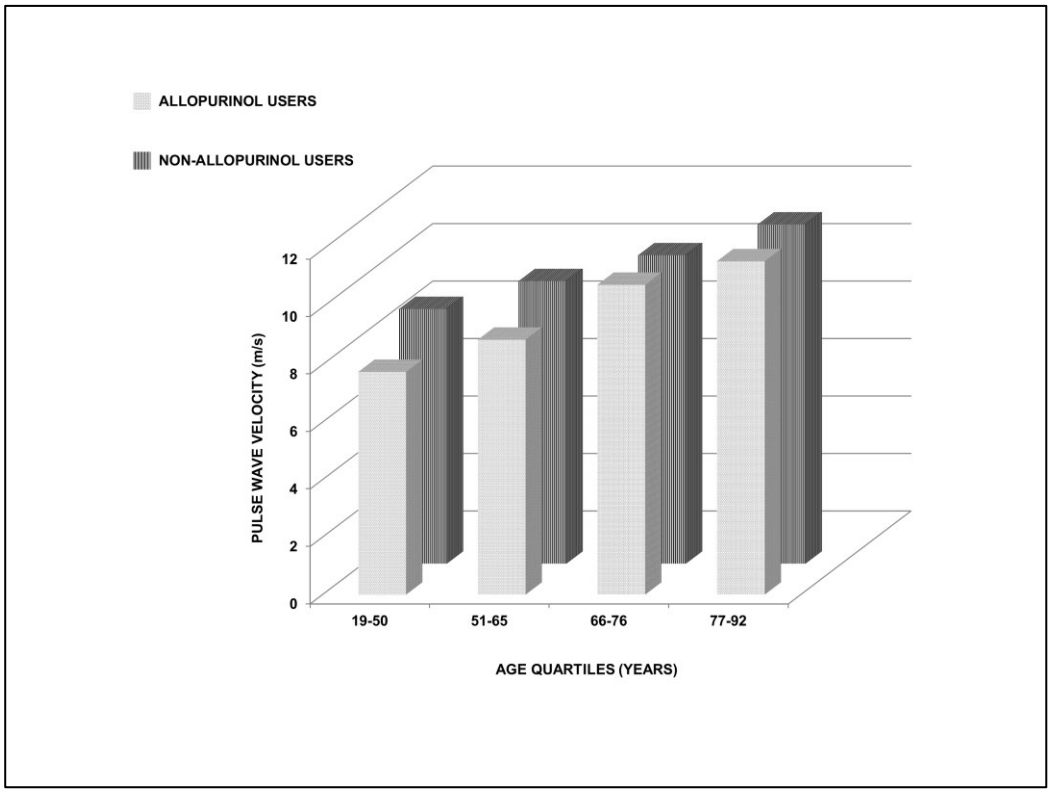



Figure 2-2: Differences in pulse wave velocity according to the use of allopurinol and age quartiles.

A linear regression model was created with cfPWV as the dependent variable. Variables which correlated with cfPWV at a p value <0.1 were included in a standard regression model. As there was strong co-linearity among the BP measures, peripheral PP was

selected from these parameters for incorporation in the regression model as it had the strongest correlation (r=0.45, p<0.001) with cfPWV. Similarly, smoking pack years was selected to adjust for the relationship between smoking history and cfPWV in the regression model. Preliminary analyses were performed to ensure no violation of the assumptions of normality, linearity and multi-collinearity. Factors entered into the model were age, gender, ethnicity, smoking pack years, diagnosis of DM, SAF level, peripheral PP, use of ACEi/ARB and use of allopurinol. Age, peripheral PP and use of allopurinol were significant independent determinants of cfPWV (Table 2-4). In the regression model, the use of allopurinol was associated with a mean reduction of cfPWV of 0.63 m/s (95% CI, -0.09 to -1.17 m/s, p=0.02). The model explained 35% of the variance in cfPWV. Substituting peripheral SBP, central SBP or central PP, for peripheral PP and substituting smoking pack years for current or previous smoking status made no appreciable difference to the model.

Table 2-4: Multiple regressions with carotid-femoral pulse wave velocity as the dependent outcome variable**.**

| | **Mean change of PWV** | **95% CI** | | **P value** |
|---|---|---|---|---|
| | | **Lower bound** | **Upper bound** | |
| **Age (/5 years)** | **0.306** | **0.225** | **0.387** | **<0.001** |
| Gender (male) | 0.423 | -0.009 | 0.856 | 0.06 |
| White ethnicity | 0.252 | -0.296 | 0.800 | 0.4 |
| Afro-caribbean ethnicity | 0.552 | -0.245 | 1.350 | 0.2 |
| Smoking pack years | 0.005 | -0.006 | 0.015 | 0.4 |
| Presence of diabetes mellitus | 0.163 | -0.261 | 0.586 | 0.5 |
| SAF (/1 a.u.) | -0.258 | -0.559 | 0.043 | 0.09 |
| **Peripheral PP (/5 mmHg)** | **0.186** | **0.121** | **0.251** | **<0.001** |
| Use of ACEI/ARB | -0.136 | -0.579 | 0.307 | 0.5 |
| **Use of allopurinol** | **-0.633** | **-1.174** | **-0.092** | **0.02** |

*Adjusted $R^2$ for model= 0.348, p<0.001.*
*Abbreviations: ACEI= angiotensin converting enzyme inhibitor; ARB= angiotensin II receptor blocker; CI= confidence interval; PP= pulse pressure, PWV= pulse wave velocity; SAF= skin autofluorescence.*

## 2.5 **Discussion**

This observational study in a prospectively recruited CKD cohort suggests that the use of allopurinol was associated with reduced arterial stiffness as measured by cfPWV, the current gold-standard measurement of arterial stiffness (86); this association was independent of age and BP. Arterial stiffness, which is a hallmark of CKD, is a well-recognised, powerful prognostic marker of CV morbidity and mortality in both the general and CKD population (58, 103, 107). Increased arterial stiffness results in higher systolic pressures, greater pressure fluctuations and leads to ventricular-arterial uncoupling, myocardial hypertrophy and fibrosis. Alterations in the extracellular matrix and endothelial dysfunction promoted by chronic inflammation, increase oxidative stress and accumulation of advanced glycation end products, vascular calcification, and activation of RAAS have been postulated to contribute to increased arterial stiffness (58, 313).

Allopurinol, a xanthine oxidase inhibitor, is commonly prescribed for patients with gout as a uric acid lowering agent. During the catalytic reaction that produces uric acid, xanthine oxidase generates ROS, which may contribute to the development of endothelial dysfunction, hypertension and vascular damage (314). Accumulating evidence from interventional studies indicates that allopurinol improves endothelial dysfunction (198, 203), lowers LV mass (198), and may slow progression of CKD and lower CV risk (201). The results of this current study suggest that some of the beneficial effect of allopurinol may occur through reducing arterial stiffness.

Even among allopurinol users, there was a high prevalence of hyperuricaemia. Although several large observational studies have reported a strong association between

hyperuricaemia and CV morbidity or mortality, the evidence for hyperuricaemia as a risk factor or risk marker of CVD is conflicting (315-323). Despite a significant association between allopurinol use and cfPWV, we found no significant direct association between serum uric acid levels and cfPWV. In a small group of patients with chronic heart failure, George et al demonstrated that the mechanism of improvement in endothelial function with allopurinol was attributable to reduced oxidative stress and not to uric acid reduction (203). CKD is known to be associated with increased oxidative stress and acute-phase inflammation, which may both contribute to increased CV risk (324). We found no significant difference in the levels of hsCRP between allopurinol users and non-allopurinol users, suggesting that inflammation was not a prominent mechanism in this association. Advanced glycation end-products (AGE) have a bi-directional relationship with oxidative stress, including studies showing that increased oxidative stress is associated with formation and accumulation of AGE (325-329). Level of tissue AGE as measured by SAF, which positively correlated with arterial stiffness, was found to be significantly lower in the allopurinol users when compared to non-allopurinol users, indicating that this biological pathway may be relevant to the link between allopurinol use and cfPWV described here.

As arterial stiffness and BP are closely related, it is possible that the effect of allopurinol on arterial stiffness may be mediated through improved BP. A recent meta-analysis showed that allopurinol is associated with a small but significant reduction in BP (330). Several hypotheses have been postulated to explain this apparent association. The antioxidant effect of allopurinol was considered to play a major role in improving endothelial function and BP regulation (330). Nonetheless, there was no clear consensus

to-date regarding the effects of oral antioxidant on arterial BP. While some demonstrated BP lowering effect of antioxidant vitamins (331, 332), others did not (333-336) and one study showed paradoxical blunting of exercise training-induced improvement in endothelial function with antioxidant administration (337). In addition to its antioxidant property, there is emerging evidence that allopurinol can block the deleterious CV effect of angiotensin II (338-340). In this current study we found a significant difference in both peripheral and central BP between allopurinol users and non-allopurinol users, despite a comparable prevalence of ACEi/ARB use and total numbers of anti-hypertensive agents between groups. However, after adjustment in a multivariate analysis, the use of allopurinol remained significantly associated with arterial stiffness. This suggests an independent association between the use of allopurinol and lower vascular stiffness. This observation is supported by an RCT of 66 patients with mild to moderate hypertension which reported a favourable effect of allopurinol on aortic compliance, independent of ACEi or thiazide-based antihypertensive therapy (341).

## 2.6 **Limitations**

There were a number of limitations in this study. Due to the observational, cross-sectional nature of the study, the association between allopurinol use and lower arterial stiffness reported here does not prove causality.

Although there were unequal distributions of gender, ethnic, BMI, current smoking status and differences in serum uric acid between the groups, these are unlikely to have resulted in bias. Male gender was associated with higher cfPWV, however despite a higher proportion of males amongst allopurinol users, use of allopurinol remained associated with

a lower cfPWV. In addition, people of African-Caribbean ethnicity had a lower cfPWV; most of the African-Caribbean participants were non-allopurinol users. The unequal distribution of gender and ethnicity between the groups was therefore unlikely to have resulted in bias against non-allopurinol use. As the number of non-white participants was small, we were unable to confidently examine the influence of allopurinol in different ethnic groups; this should be an area for future study. Although there were differences in BMI and serum uric acid level between the groups, there parameters did not have a significant bivariate association with cfPWV; hence, they were unlikely to confound the findings. Smoking history is known to have significant influence on arterial stiffness and there were a higher proportion of current smokers in the allopurinol non-user group. In addition, the comparatively lower peripheral and central pressures in the allopurinol user group might have contributed to lower cfPWV as BP is a strong determinant of arterial stiffness. However, after adjusted for haemodynamic parameters and smoking history in the regression model, use of allopurinol remained associated with lower cfPWV.

Although all available confounding variables were included in this study, there may be other potential unknown confounders as the biology of vascular disease in CKD is complex. The measurement of hsCRP was performed only at single time-point rather than the two time-points two weeks apart recommended by the American Heart Association (342). We did not have measurements of endothelial dysfunction, which is closely linked to arterial stiffness and CKD (58). Finally, encouraging results have been reported on an effect of allopurinol in improving renal function in patients with asymptomatic hyperuricaemia (343) or delaying disease progression in patients with CKD (201, 344).

However, due to the cross-sectional nature of the data we were unable to examine this relationship.

This cross-sectional study did not demonstrate statistically significant association between PWV and levels of renal function. Though majority of the studies to date have reported a direct linear, negative relationship between GFR and arterial stiffness (65, 77, 80), McIntyre et al similarly did not find eGFR as an independent determinant of arterial stiffness in the cross-sectional study of 1,717 patients with CKD stage 3 but concluded age and traditional CV risk factors as the strongest determinants (345). The unique inclusion criteria of RIISC study might provide much explanation to such finding. As stated in section 2.2.2., the RIISC study enrolled patients with CKD stage 3-5, however, those with CKD stage 3 would only be included if they were deemed to be at high risk of renal disease progression, which was defined as those with a declining MDRD eGFR of ≥5 ml/min/year or ≥10 ml/min/5years or a uACR ≥70 mg/mmol on three consecutive occasions. As urinary albumin excretion has been shown to be independently associated with greater arterial stiffness (83), such unique selection of patients with CKD stage 3 most possibly have affected and confounded the association between arterial stiffness and eGFR in this study population.

## 2.7 **Conclusion**

In summary, the data shown here suggests that allopurinol is independently associated with lower arterial stiffness in patients with progressive CKD. This adds to the accumulating evidence of the favourable effect of allopurinol on CV outcomes in a well-defined CKD cohort and indicates one mechanism by which this may occur. This study provides further

justification for a large definitive RCT examining the therapeutic potential of allopurinol to reduce CV risk in people with CKD.

# CHAPTER 3 SYSTEMATIC REVIEW AND META-ANALYSIS OF THE CARDIOVASCULAR EFFECTS OF MINERALOCORTICOID RECEPTOR ANTAGONISTS IN PATIENTS WITH CHRONIC KIDNEY DISEASE

## 3.1 Introduction

The importance of the RAAS in the progression of renal disease and in the development of CV disease amongst the CKD population is widely recognised (227, 346). The renal and CV benefits of inhibition of the RAAS have been demonstrated in multiple large trials of ACEi and ARB, largely attributed to the prevention of the multiple adverse effects of angiotensin II (347).

Strong evidence suggests that ACEi and ARB drugs do not effectively inhibit aldosterone production in all patients and that aldosterone may also be a mediator of renal and CV damage in patients with CKD (227). Mineralocorticoid receptors (MR) are present in the brain, heart and blood vessels as well as the kidney, and there is evidence of aldosterone production within these tissues (348). Local MR activation by aldosterone causes numerous pathological effects on the CV system including endothelial injury, inflammation, oxidative stress and fibrosis in the heart and vasculature, as well as the development of hypertension and autonomic dysfunction (58, 348). This evidence has led to the suggestion that potentially someday all renal patients with be on an MRA as a "renal aspirin" (349).

However, there is still a reluctance to use these agents in patients with CKD particularly because of the risk of further deterioration in renal function and the risk of dangerous hyperkalaemia (347). Although the effects of MRA on proteinuria have been the subject of recent meta-analyses, the potential benefits of MRA on CV parameters and mortality in patients with CKD are not clear (245, 246). This systematic review therefore examined the actions of MRA on surrogate markers of CV disease as well as major patient level CV end-points in patients with CKD.

## 3.2 **Methods**

This systematic review and meta-analysis was performed in accordance with the PRISMA statement (350). The protocol and detailed methodology for this systematic review was registered with the International Prospective Register of Systematic Reviews (PROSPERO; CRD42013006795) (351). The following electronic databases and trial registers were searched from their conception to September 2013: MEDLINE, EMBASE, Trip Database, Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Renal Group specialised register, Current Controlled Trials and ClinicalTrials.gov. References of included articles and relevant review articles were hand-searched. Search terms including both medical subject headings (MeSH) and their derivatives: mineralocorticoid receptor antagonist, spironolactone, eplerenone, chronic kidney disease, and chronic renal failure. All searches were limited to human studies.

### 3.2.1 Type of Studies

All fully published RCTs examining the CV effects of both spironolactone and eplerenone in patients with CKD were included. Cohort studies, case series and case reports were

excluded from the review owing to the high potential for bias in these study designs. Crossover studies were included provided there was evidence of a washout period and/or exclusion of a carry-over effect. All analyses were repeated excluding crossover studies. There was no language restriction.

### 3.2.2 Types of Participants

Studies enrolling adult participants, with CKD stages 1-5, as defined by the KDOQI guidelines, including dialysis patients and kidney transplant recipients (352).

### 3.2.3 Types of Interventions

The review included studies of both non-selective (spironolactone) and selective (eplerenone) MRAs with or without concomitant use of ACEi and/or ARB given for at least 4 weeks.

### 3.2.4 Types of Outcome Measures

Data on the effects of MRA on the following outcome measures were examined: systolic and diastolic BP; parameters of arterial stiffness including PWV; endothelial function and oxidative stress; carotid intima-media thickness (CIMT); LV ejection function; LV mass; CV morbidity and mortality; hyperkalaemia (serum potassium> 5.5 mmol/L); decline in renal function and other adverse events including gynecomastia.

### 3.2.5 Data Collection

The selection of relevant articles was performed in stages. The initial literature search, which broadly applied the inclusion criteria using the search strategy or search terms, was performed to identify any potentially relevant articles. Two reviewers (Dr Charles Ferro and the author) independently screened retrieved articles and discarded studies that did not meet the inclusion criteria. Studies and reviews that might include relevant data or information on trials were retained initially. Duplicates studies were removed. Both reviewers further reviewed the eligibility of the selected studies in abstract form, or if appropriate, in full text, independently by assessing if the inclusion criteria and outcome measures were met. The reasons for excluding studies were documented. The selected and excluded articles between the two reviewers were compared. Disagreements regarding article selection, data extraction and quality assessment were discussed between reviewers until consensus on inclusion was reached or by consultation with a third party (Dr Adnan Sharif).

Further data extraction of the eligible studies was carried out by the two reviewers independently. Information regarding trial design, patients' characteristics (age, comorbidities, CKD stages), intervention drugs, dosage, treatment duration, co-intervention, follow-up duration, withdrawal rates and type of outcome measures were recorded on a standard collection form (see Appendix 3-1). Non-English articles were translated into English before data extraction. In the case of multiple publications of the same trial, with different data sets, all outcomes and results were grouped together and single data extraction was performed on the most complete dataset.

### 3.2.6 Study Quality

The risk of bias assessment tool developed by Cochrane Renal Group (353) was applied to each study. The reviewers independently assessed the quality of each included study on selection bias (sequence generation, allocation concealment), detection bias (personnel and participant, outcome assessors), attrition bias (incomplete outcome data), reporting bias (selective outcome reporting) and other potential biases (Appendix 3-2). Disputes were settled by discussion with a third party (Dr Adnan Sharif).

### 3.2.7 Statistical Assessment

Meta-analysis was conducted to generate pooled estimates of the outcomes using RevMan 5.2 software (©2012, The Cochrane Collaboration, UK). Data were pooled and a random effect model was used as summary effect measure. Relative risk ratio or weighted mean difference with accompanying 95% CI were used to report individual and summary effect measures for dichotomous or continuous data, respectively. $\chi^2$ tests for heterogeneity were performed to examine if the degrees of freedom were greater than the Cochran Q statistic, with $\alpha$ of above 0.05 as statistical significance. In addition, we also calculated the $I^2$ statistic to provide the estimated percentage of heterogeneity observed. $I^2$ values of 25%, 50% and 75% corresponded to low, medium and high levels of heterogeneity. Any heterogeneity was further explored. When appropriate, subgroups of different MRAs (selective or non-selective), comparator (active or placebo/standard treatment) and concomitant ACEi and/or ARB were analysed. A two-sided p-value of $<0.05$ was considered significant for all analyses.

## 3.3 **Results**

### 3.3.1 Search Results

A total of 2,823 articles were identified, of which 66 articles met the general inclusion criteria. Full-text assessment of these articles identified 29 eligible studies (31 articles) (140, 248, 249, 354-381) (Table 3-1), enrolling a total of 1,581 patient for qualitative synthesis and 28 eligible studies enrolling a total of 1,548 patient for meta-analysis (Figure 3-1).

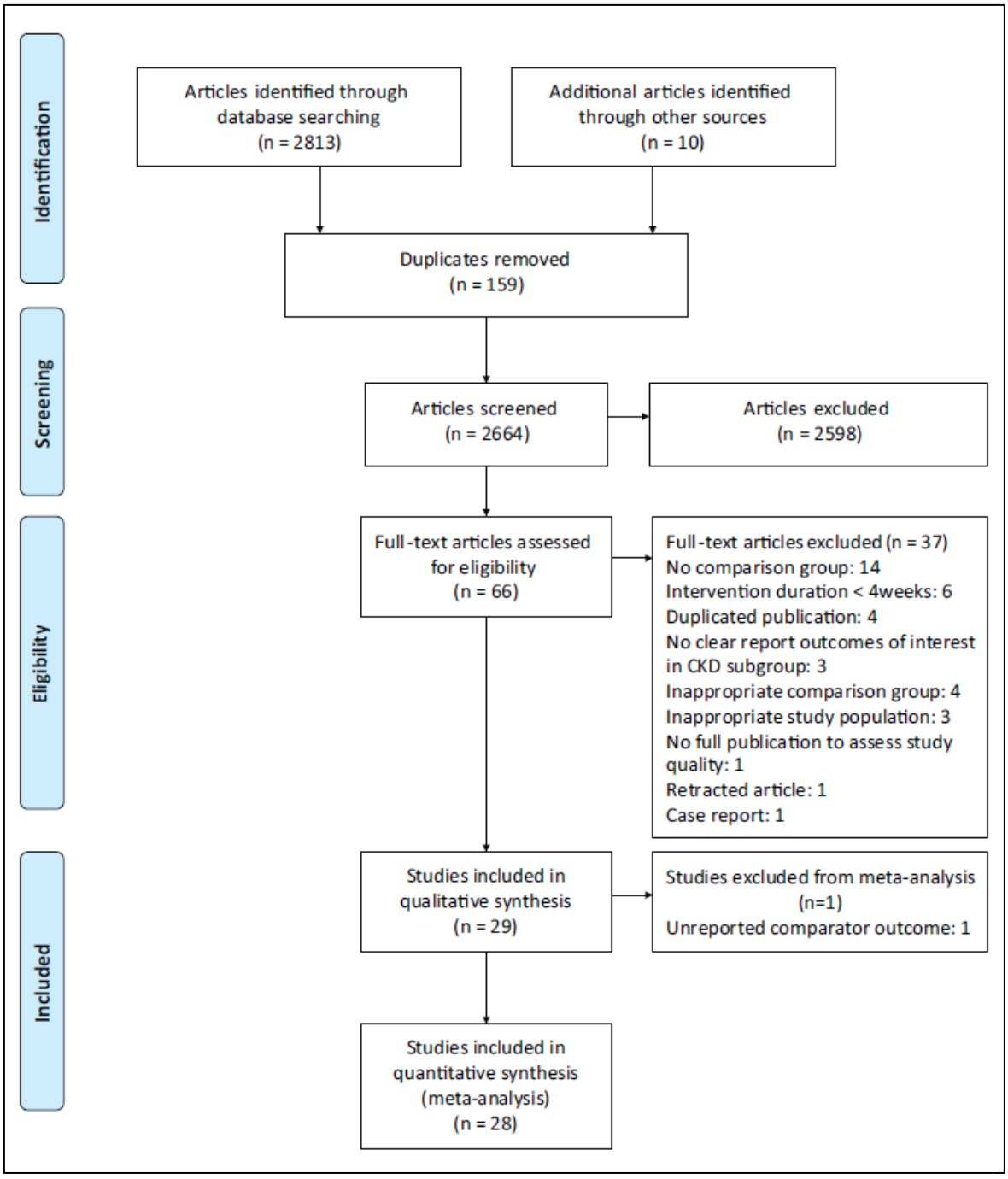



Figure 3-1: Study flow diagram of the systematic review and meta-analysis of the cardiovascular effects of mineralocorticoid antagonist in patients with chronic kidney disease

Table 3-1: Characteristics of the populations and interventions of the included trials

| Study | Type of study | Study population | Intervention(s) | Also on ACEi/ARB | No. of patients | Study duration (weeks) | Outcomes measured (Underlined parameters represent primary outcome) |
|---|---|---|---|---|---|---|---|
| Abolghasmi et al, 2011 (354) | RCT, double-blinded, parallel. | CKD (eGFR 25-50 ml/min) with resistant hypertension | Spironolactone 25- 50 mg/d vs. Placebo | Yes | 41 | 12 | BP, serum $K^+$, creatinine, serum and urinary $Na^+$ |
| Bianchi et al, 2006 (355) | RCT, open-label, parallel. | Non-diabetic CKD (eGFR 34-116 ml/min) and proteinuria (1.0-3.9 g/g creatinine) | Spironolactone 25 mg/d | Yes | 165 | 52 | BP, serum $K^+$, creatinine, proteinuria, eGFR |
| Boesby et al, 2011 (356) | RCT, open-label, cross-over. | Non-diabetic CKD (CrCl 24-195 ml/min) with proteinuria >500 mg/d or albuminuria >300mg/d | Eplerenone 25-50 mg/d | No | 42 | 8 | BP, serum $K^+$, creatinine, albuminuria |
| Boesby et al, 2013 (357) | RCT, open-label, parallel. | CKD stage 3-4 with BP >130/80 mmHg or use of anti-hypertensive. | Eplerenone 25-50 mg/d | No | 54 | 24 | cfPWV, AIx, ambulatory arterial stiffness index, BP, serum $K^+$, creatinine, proteinuria, eGFR |
| Chrysostomou et al, 2006 (358) | RCT, double-blinded followed by open-label, parallel. | CKD with creatinine < 200 µmol/L but proteinuria > 1.5g/d | Ramipril 5mg/d vs. Ramipril 5mg/d + Irbesartan 150mg/d vs. Ramipril 5mg/d + Spironolactone 25mg/d vs. Ramipril 5mg/d + Irbesartan 150mg/d + Spironolactone 25mg/d | Yes | 41 | 52 | Proteinuria, BP, eGFR |
| Edwards et al, 2009, 2010, 2012 (140, 248, 249) | RCT, double-blinded, parallel. | Non-diabetic CKD stage 2-3 | Spironolactone 25mg/d | Yes | 112 | 40 | 24 hour ambulatory BP, cfPWV, PWA, LV mass, LV function, serum $K^+$, creatinine, albuminuria, eGFR, N-terminal-pro-B-type natriuretic peptide, aminoterminal propeptide of type III procollagen |

| Study | Type of study | Study population | Intervention(s) | Also on ACEi/ARB | No. of patients | Study duration (weeks) | Outcomes measured (Underlined parameters represent primary outcome) |
|---|---|---|---|---|---|---|---|
| Epstein et al, 2006 (359) | RCT, double-blinded, parallel. | Type 2 DM with albuminuria (uACR ≥ 50mg/g) and CrCl > 70 ml/min | Enalapril 20mg/d vs. Enalapril 20mg/d + Eplerenone 50mg/d vs. Enalapril 20mg/d + Eplerenone 100mg/d | Yes | 268 | 12 | Albuminuria, incidence of hyperkalaemia, BP, eGFR |
| Esteghamati et al, 2013 (360) | RCT, open-label, parallel. | DM with uACR ≥ 30 mg/d and eGFR>30 ml/min/1.73m$^2$ | Spironolactone 25mg/d + ARB vs.ACEi+ ARB | Yes | 136 | 78 | BP, albuminuria, serum creatinine, $K^+$, eGFR |
| Furumatsu et al, 2008 (361) | RCT, open-label, parallel. | Non-DM CKD with persistent proteinuria (>0.5 g/d), serum creatinine <3.0 mg/dl (or CrCl > 30 ml/min), BP < 130/80 mmHg | Spironolactone 25mg/d + Enalapril 5mg + Losartan 50mg/d vs. Trichlormethiazide 1mg/d (if Cr<1.8 mg/dl) or Furosemide (if Cr<1.8 mg/dl + Enalapril 5mg + Losartan 50mg/d | Yes | 32 | 12 | BP, serum $K^+$, creatinine, PAI-1, PRA, AII, PAC, proteinuria and urinary Type IV collagen |
| Guney et al, 2009 (362) | RCT, parallel. | Non-DM CKD stage 1-3, BP <130/80 mmHg and persistent proteinuria (> 0.5 mg/mg). | Spironolactone 25mg/d; | Yes | 24 | 26 | BP, serum $K^+$, creatinine, PAC, proteinuria and urinary TGF-β1 |
| Hase et al, 2013 (363) | RCT, open-label, parallel. | T2DM with uACR ≥ 100mg/g, *creatinine ≥ 2mg/dl excluded | Spironolactone 25mg/d vs. Trichlormethiazide 2mg/d | Yes | 36 | 24 | BP, serum $K^+$, creatinine, albuminuria |
| Joffe et al, 2007 (364) | RCT, double-blinded, cross-over. | DM with albuminuria (uACR ≥ 30 mg/g) and Creatinine < 1.5 mg/dl | Eplerenone 50mg/d vs. Hydrochlorothiazide 12.5mg/d + potassium 10mEq/d | Yes | 16 | 6 | BP, serum $K^+$, creatinine, proteinuria, adenosine-stimulated myocardial perfusion reserve, brachial artery reactivity, peripheral arterial tonometry |
| Lizakowski et al, 2013 (365) | RCT, double-blinded, cross-over. | Non-DM CKD stage 1-3, proteinuria > 500mg/d | Eplerenone 50mg/d + Telmisartan 80mg/d vs. Aliskerin 300mg/d + Telmisartan 80mg/d vs.Telmisartan 160mg/d; | Yes | 18 | 8 | 24 hour ambulatory BP, serum $K^+$, creatinine, eGFR, urinary TGF-β1, plasma concentration of prorenin and renin |

| Study | Type of study | Study population | Intervention(s) | Also on ACEi/ARB | No. of patients | Study duration (weeks) | Outcomes measured (Underlined parameters represent primary outcome) |
|---|---|---|---|---|---|---|---|
| Matsumoto et al, 2006 (366) | RCT (2:1 ratio), parallel. | DM nephropathy with UAE > 30 mg/g *creatinine > 1mg/dl excluded | Spironolactone 50mg/d; Amlodipine 2.5mg/d | No | 33 | 12 | BP, serum $K^+$, creatinine, serum adiponectin, visfatin, TNF-α, plasma PAI-1, hsCRP, sCD40L, BNP |
| Mehdi et al, 2009 (367) | RCT, double-blinded, parallel. | DM nephropathy with uACR ≥ 300mg/g and hypertensive. | Spironolactone 25mg/d vs. Losartan 100mg/d vs. Placebo | Yes | 80 | 48 | Ambulatory BP, serum $K^+$, creatinine, albuminuria, $HbA_{1c}$ |
| Meiracker, et al, 2006 (368) | RCT, double-blinded, parallel. | DM with uACR > 20mg/mmol and creatinine <265 µmol/L | Spironolactone 25-50mg/d vs. Placebo | Yes | 59 | 52 | BP, serum $K^+$, creatinine, proteinuria, $HbA_{1c}$ |
| Morales et al, 2009 (369) | RCT, open-label, cross-over. | Obesity (BMI > 30 $kg/m^2$) with proteinuria > 0.5g/d. | Eplerenone 25 mg/d vs. Lisinopril 10 mg/d + Candesartan 16mg/d vs. Lisinopril 20mg/d | Yes | 12 | 6 | BP, serum $K^+$, creatinine, proteinuria, plasma renin and aldosterone level |
| Nielsen et al, 2012 (370) | RCT, double-blind, cross-over. | Type 1 DM with microalbuminuria (30-300 mg/d) | Spironolactone 25 mg/d; Placebo | Yes | 21 | 8 | 24 hour BP, serum $K^+$, creatinine, eGFR; albuminuria, markers of tubular damage (urinary LFABP, NGAL, KIM1) |
| Nielsen et al, 2013 (371) | RCT, double-blinded, cross-over. | Type 1 or type 2 DM with micro- or macroalbuminuria | Spironolactone 25 mg/d; Placebo | Yes | 69 | 8 | Inflammatory markers, endothelial dysfunction (sE-selectin, s-ICMI, s-VCAMI, VWF, p-selectin, s-thrombomodulin) and NT-proBNP |
| Rossing et al, 2005 (372) | RCT, double-blinded, cross-over. | Type 2 DM nephropathy with albuminuria > 300 mg/d and GFR> 30 ml/min/1.73$m^2$ | Spironolactone 25 mg/d; Placebo | Yes | 21 | 8 | 24-hour ambulatory BP, serum $K^+$, eGFR, albuminuria |
| Saklayen et al, 2008 (373) | RCT, double-blinded, cross-over. | DM nephropathy with creatinine < 2mg/dl and $K^+$ < 5.0 mEq/L | Spironolactone 25-50 mg/d; Placebo | Yes | 30 | 12 | 24-hour ambulatory BP, serum $K^+$, eGFR, proteinuria |

| Study | Type of study | Study population | Intervention(s) | Also on ACEi/ARB | No. of patients | Study duration (weeks) | Outcomes measured (Underlined parameters represent primary outcome) |
|---|---|---|---|---|---|---|---|
| Schjoedt et al, 2005 (374) | RCT, double-blinded, cross-over. | Type 1 DM with albuminuria >300 mg/d and GFR > 30 ml/min/1.73m$^2$ and $K^+$ < 4.5 mmol/L | Spironolactone 25 mg/d vs. Placebo | Yes | 22 | 8 | 24-hour ambulatory BP, serum $K^+$, eGFR, HbA1c, albuminuria, plasma renin and aldosterone levels |
| Taheri et al, 2009 (375) | RCT, double-blinded, parallel. | Haemodialysis with heart failure (NYHA III-IV) and EF ≤ 45% | Spironolactone 25 mg thrice weekly post-dialysis vs. Placebo | Yes | 16 | 24 | Serum $K^+$, EF and LV mass |
| Taheri et al, 2012 (376) | RCT, double-blinded, parallel. | CAPD with heart failure (NYHA III-IV and EF ≤ 45%) with $K^+$ < 5.5 mEq/l | Spironolactone 25 mg alternate days vs. Placebo | Yes | 18 | 24 | Serum $K^+$ and EF |
| Takebayashi et al, 2006 (377) | RCT (5:3 ratio), parallel | Type 2 DM nephropathy with UAE > 30 mg/g creatinine. | Spironolactone 50 mg/d; Amlodipine 2.5 mg/d | No | 40 | 12 | Urinary 8-iso-prostaglandin F2α, urinary MCP-1 and albuminuria |
| Tylicki et al, 2008 (378) | RCT, open-label, cross-over. | Non-DM CKD, proteinuria > 0.3 g/d and GFR > 45 ml/min | Spironolactone 25 mg/d; None | Yes | 18 | 8 | 24-hour ambulatory BP, serum $K^+$, creatinine, eGFR, proteinuria, PRA, urinary NAG, α1m, PIIINP |
| Vukusich et al, 2010 (379) | RCT, double-blinded, parallel | Non-DM HD with no residual renal functionand $K^+$ < 6 mEq/L | Spironolactone 50 mg thrice weekly post-HD vs. Placebo | No | 66 | 104 | BP, serum $K^+$, CIMT |
| Zheng et al, 2011 (380) | RCT, parallel. | DM, albuminuria > 300 mg/d and creatinine < 1.7 mg/dl | Spironolactone 20 mg/d + Benazepril 10mg/d vs. Benazepril 10mg/d | Yes | 40 | 12 | Serum $K^+$, creatinine, proteinuria, |
| Ziaee et al, 2013 (381) | RCT, parallel. | Type 2 DM with microalbuminuria, creatinine < 2 mg/dl and $K^+$ < 5.5 mmol/l | Spironolactone 25 mg/d + Enalapril 25 mg b.d. vs. Enalapril 25 mg b.d. | Yes | 51 | 12 | BP, serum $K^+$, creatinine, GFR, albuminuria, |

Abbreviation: AII= angiotensin II; ACEi= angiotensin converting enzyme inhibitor; AIx= augmentation index; ARB= angiotensin II receptor blocker; α1m= $\alpha_1$-microglobulin; b.d.= twice daily; BMI= body mass index; BNP= B-type natriuretic protein; BP= blood pressure; CAPD= patients on continuous ambulatory peritoneal dialysis; cfPWV= carotid-femoral pulse wave velocity; CKD= chronic kidney disease; CMR= cardiovascular magnetic resonance; Cr= serum creatinine; CrCl = creatinine clearance; DM= diabetes mellitus; EF= ejection fraction; eGFR= estimated glomerular filtration rate; GN= glomerulonephritis; $HbA_{1c}$ = haemoglobin $A_{1c}$; HD= patients on haemodialysis; hsCRP= high sensitivity c-reactive protein; $K^+$= potassium; KIM-1= kidney injury molecule 1; LFABP= liver-type datty-acid binding protein; LV= left ventricular; LVMI= left ventricular mass index; MCP-1= monocyte chemoattractant protein 1; $Na^+$= sodium; NAG = N-acetyl-β-D-glucosaminidase; NGAL= neutrophil gelatinase associated lipocalin; NT-proBNP= N-terminal-pro brain natriuretic peptide; NYHA= New York Heart association; PAC= plasma aldosterone concentration PAI-1= plasminogen activator inhibitor-1; PIIINP = amino-terminal propeptide of type III procollagen; PRA= plasma renin activity; pt= participants; PWA= pulse wave analysis; RCT= randomised controlled trial, SBP= systolic blood pressure; sE-selectin= soluble E-selectin; s-ICMI= soluble-intercellular adhesion molecule; s-VCAMI= soluble vascular cell adhesion molecule I; TNF-α = tumour necrosis factor alfa; uACR= urine albumin:creatinine ratio; UAE= urine albumin excretion; VWF= von Willebrand factor

### 3.3.2 Trial Characteristics

The characteristics of included studies are detailed in Table 3-1. Ten were crossover studies. One study examined patients on peritoneal dialysis (376), two studies examined patients on haemodialysis (375, 379) and the remaining studies examined patients with CKD. All but two of these studies (354, 356) excluded patients with advanced CKD (eGFR<30 ml/min/1.73m$^2$). Even for the two studies which included patients with advance CKD, it was not clear how many patients with such level of renal function were actually recruited. This review did not identify any eligible study involving renal transplant recipients. Spironolactone was used in 23 studies and eplerenone in six. Active comparator arms involving the use of additional antihypertensive agents were noted in 13 studies with the rest involving MRA treatment being compared against placebo or standard care. Concomitant use of ACEi and/or ARB was reported in 24 studies. Study duration ranged from 8 to 104 weeks and study population ranged from 12 to 268 participants. None of the studies were powered to detect hard primary outcomes. Proteinuria or albuminuria was the primary outcome in 17 of the studies with CV outcomes as secondary end-points. Risks of bias in the included studies are shown in Appendix 3-3. Most of the studies did not report enough information for adequate assessment of risk on most of the parameters assessed.

### 3.3.3 Effects of Interventions

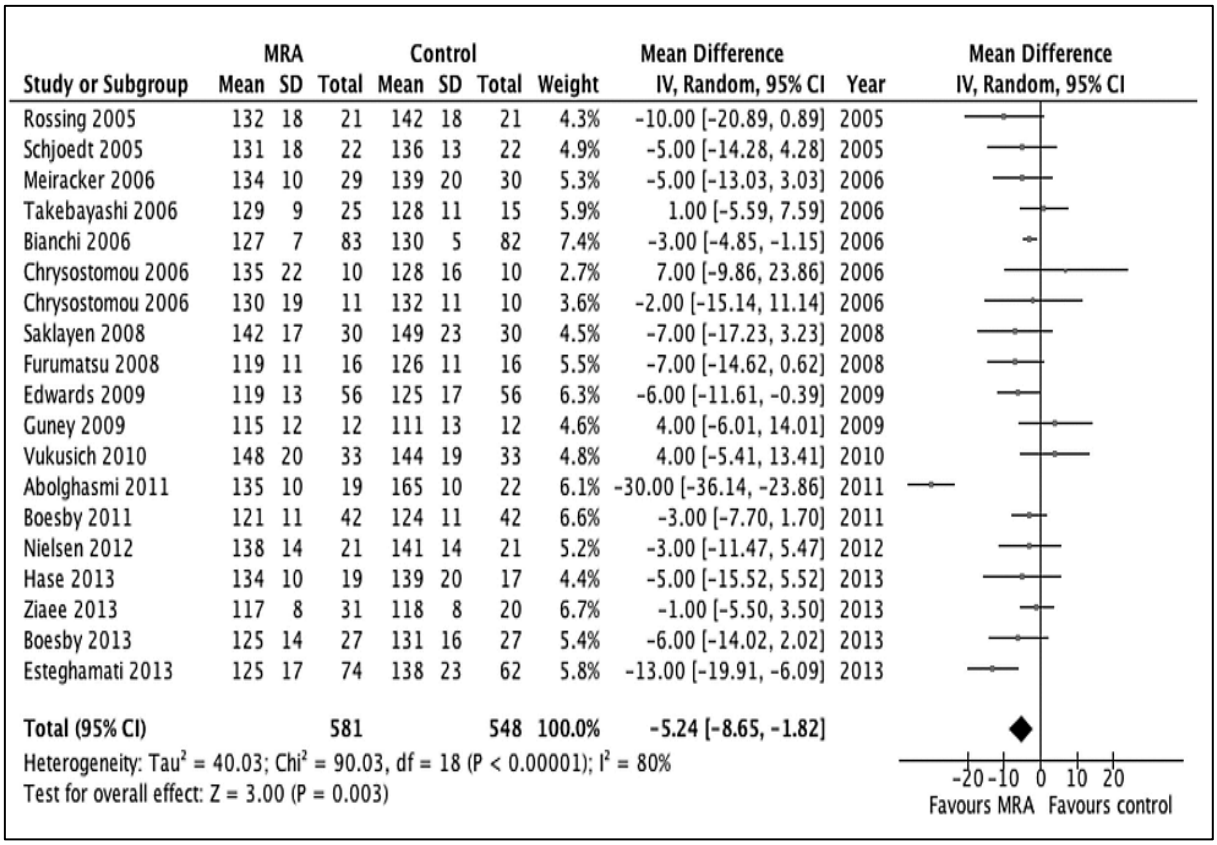
#### *3.3.3.1 End of treatment blood pressure*

Twenty-one studies reported data on BP suitable for analysis. Three protocols required the use of additional antihypertensive agents to be initiated during the study in order to achieve a BP <130/80 mmHg in both the intervention and control arms (359, 364, 378) and were therefore

excluded from the analyses leaving 18 RCTs with 1,129 patients. Spironolactone was used in 16 studies and eplerenone in two.

Overall, there was a significant reduction of SBP with MRA (-5.24, 95% CI: -8.65, -1.82 mmHg, p=0.003; Figure 3-2) although there was high heterogeneity ($\chi^2$=90.03, p<0.001; $I^2$=80%). Exclusion of the only study examining the effects of MRA in patients with CKD and resistant hypertension (354) resulted in a small change in treatment effect (-3.56, 95% CI: -5.30, -1.83 mmHg, p<0.001) but reduced the heterogeneity ($\chi^2$=20.74, p=0.2; $I^2$=18%). Exclusion of crossover studies made little difference (-3.56, 95% CI: -5.85, -1.27 mmHg, p=0.002) with low-medium heterogeneity ($\chi^2$=18.61, p=0.1; $I^2$=36%). Overall, MRA lowered SBP (-3.31, 95% CI: -4.78, -1.84 mmHg; p<0.001) versus placebo with low heterogeneity ($\chi^2$=8.06, p=0.6; $I^2$=0%) but not when compared with another anti-hypertensive agent (-3.77, 95% CI: -8.25, 0.71 mmHg, p=0.1) although this analysis had moderate heterogeneity ($\chi^2$=12.66, p=0.05; $I^2$=53%).

Spironolactone reduced SBP (-3.56, 95% CI: -5.61, -1.51 mmHg, p<0.001) with low heterogeneity ($\chi^2$=20.29, p=0.2; $I^2$=26%); it was more effective than placebo (-3.23, 95% CI: -5.19, -1.28 mmHg, p=0.001; $I^2$=6%) and active comparators (-3.64, 95% CI: -6.36, -0.91 mmHg, p=0.009; $I^2$=38%). Analysis of the two studies using eplerenone suggested a SBP-lowering effect but this failed to achieve statistical significance (-3.77, 95% CI: -7.83, 0.29 mmHg, p=0.07; $I^2$=0%).

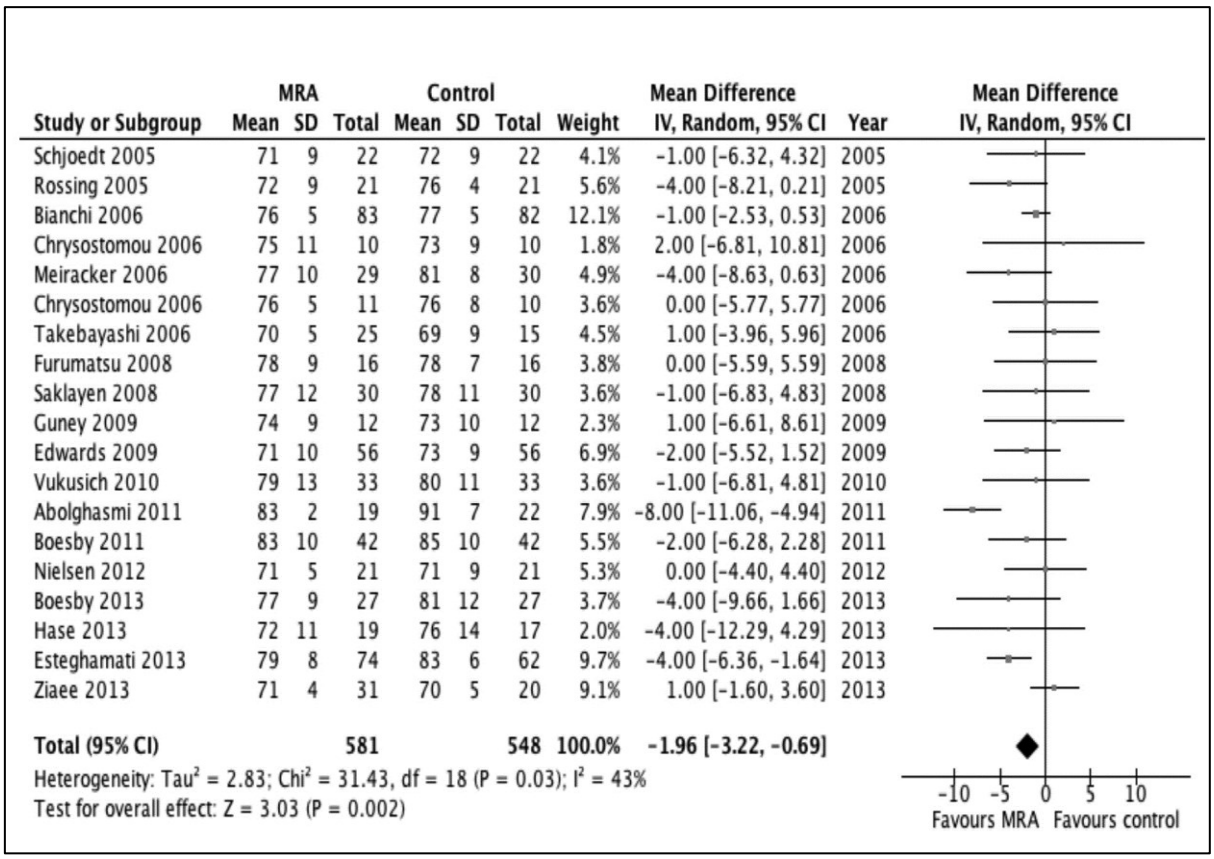



*Abbreviation: MRA: mineralocorticoid receptor antagonist; CI: confidence interval; IV: inverse variance.*

Figure 3-2: Effect of mineralocorticoid receptor antagonists on systolic blood pressure.

Similar results were noted with respect to DBP (Figure 3-3). Overall, there was a significant reduction of DBP (-1.96, 95% CI: -3.22, -0.69 mmHg, p=0.002) although there was moderate heterogeneity ($\chi^2$=31.43, p=0.03; $I^2$=43). Heterogeneity was significantly reduced ($\chi^2$=15.02, p=0.6; $I^2$=0%) by the exclusion of the only study on patients with resistant hypertension (354) with only a small change on the treatment effect (-1.42, 95% CI: -2.29, -0.55 mmHg, p=0.001). Further exclusion of crossover studies made little difference (-1.37, 95% CI: -2.44, -0.30 mmHg, p=0.01) with low heterogeneity ($\chi^2$=13.04, p=0.4; $I^2$=8%). Against placebo, MRA lowered DBP (-1.62, 95% CI: -2.73, -0.51 mmHg, p=0.004; $\chi^2$=5.05, p=0.9; $I^2$=0%) but not when compared with another anti-hypertensive agent (-0.84, 95% CI: -3.07, 1.40 mmHg, p=0.4; $\chi^2$=10.21, p=0.1; $I^2$=41%).

Spironolactone reduced DBP (-1.33, 95% CI: -2.23, -0.43 mmHg, p=0.004; $I^2$=0%); it was more effective than placebo (-1.39, 95% CI: -2.53, -0.26 mmHg, p=0.02; $\chi^2$=3.88, p=0.9; $I^2$=0%) but not more effective than an active comparator (-0.58, 95% CI: -3.00, 1.87 mmHg: p=0.5; $\chi^2$=9.77, p=0.08; $I^2$=41%). Analysis of the two studies using eplerenone suggested a non-significant DBP-lowering effect (-2.73, 95% CI: -6.14, 0.68 mmHg, p=0.1; $\chi^2$=0.31, p=0.6; $I^2$=0%).




*Abbreviation: MRA: mineralocorticoid receptor antagonist; CI: confidence interval; IV: inverse variance.*

Figure 3-3: Effect of mineralocorticoid receptor antagonists on diastolic blood pressure.

### 3.3.4 Arterial Stiffness

Two studies examined PWV as the primary outcome (140, 357). In a randomised, open-label study of 46 patients with CKD stage 3-4, 24-weeks of treatment with eplerenone did not

significantly reduce PWV or BP (357). Nonetheless, in a larger, double-blinded, placebo-controlled RCT of 112 patients with CKD Stages 2-3, treatment with spironolactone for 40 weeks significantly reduced PWV (-0.8 ± 1.0 vs. -0.1 ± 0.9 m/s, $p<0.01$) and increased aortic distensibility with a significant reduction in BP (140).

### 3.3.5 Endothelial Function and Oxidative Stress

Two studies examined the actions of MRA on endothelial function with neither study showing a significant effect (364, 371). Takebayashi et al demonstrated a significant reduction in 8-iso-prostaglandin F2α, a marker of oxidative stress, with spironolactone while no significant change occurred with amlodipine 2.5mg daily after 12 weeks of treatment (377).

### 3.3.6 Carotid Intima-Media Thickness

Only one study examined the actions of MRA on CIMT. Spironolactone thrice weekly post-dialysis was shown to significantly reduce the progression of CIMT after 2 years as compared to placebo (379).

### 3.3.7 Left Ventricular Ejection Function and Mass

Among patients on haemodialysis or peritoneal dialysis with a clinical diagnosis of heart failure (New York Heart Association III-IV and ejection fraction <45%), spironolactone thrice weekly in addition to ACEi or ARB was shown to significantly improve LV ejection fraction after 24 weeks as compared to placebo (375, 376). Whilst there was no detectable difference in LV ejection fraction between those receiving spironolactone and placebo in a

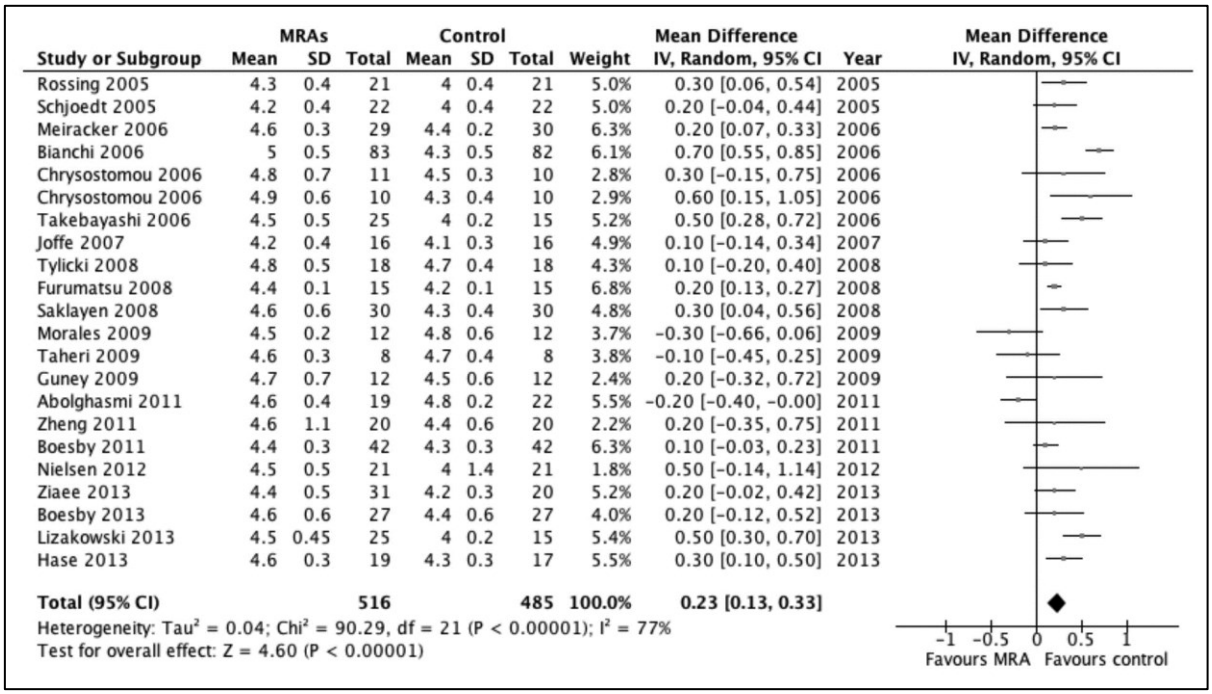
RCT of 112 patients with CKD stage 2-3 without a clinical diagnosis of heart failure and with normal LV function, Edwards et al demonstrated significant improvements in other indices of systolic and diastolic function including LV long-axis systolic function, torsion, myocardial deformation and markers of LV relaxation and suction in the spironolactone group (249). In patients with diabetic nephropathy, myocardial perfusion reserve improved after 6 weeks of eplerenone while there was no change in the control group treated with hydrochlorothiazide (364). Three RCTs examined the effect of MRA on brain natriuretic peptide with all studies reporting significant reductions (249, 366, 371). Two placebo-controlled studies examining the actions of MRA on LV mass reported a reduction with the use of spironolactone after 40 weeks (-14 ± 3 g, $p<0.01$) (140) and after 6 months (-8 ± 4 g, $p=0.02$) (375).

### 3.3.8 End of Study Serum Potassium and Hyperkalaemia Events

Twenty-one studies (1015 patients) reported end of study serum potassium. Overall, the use of MRA was associated with an increase in serum potassium (serum $K^+ > 5.5$ mmol/L) (0.23, 95% CI: 0.13, 0.33 mmol/L, $p<0.001$) but with high heterogeneity ($\chi^2=90.29\%$, $p<0.001$; $I^2=77\%$; Figure 3-4). Two studies used additional potassium supplementation or potassium binders (361, 364). Exclusion of these two studies made little difference to the result (0.24, 95% CI: 012, 0.36 mmol/L; $p<0.001$) with persistent high heterogeneity ($\chi^2=87.80$, $P<0.001$, $I^2=78\%$). Exclusion of crossover studies did not materially affect the result (0.25, 95% CI: 0.11, 0.40 $p<0.001$: $\chi^2=67.48$, $p<0.001$, $I^2=82\%$). Excluding three studies in which MRA was not co-administered with an ACEi and/or ARB did not significantly affect the result (0.22, 95% CI: 0.11, 0.34 mmol/L; $p<0.001$: $\chi^2=80.48$, $p<0.001$, $I^2=78\%$). Spironolactone (0.26, 95% CI: 0.14, 0.37 mmol/L; $p<0.001$) but not eplerenone (0.14, 95% CI: -0.08, 0.36 mmol/L;

p=0.2) increased end of study serum potassium although both analyses had high heterogeneity ($\chi^2$=69.45, p<0.001; $I^2$=77% & $\chi^2$=18.21, p=0.001; $I^2$=78% respectively).

Twenty-six studies (1619 patients) reported episodes of hyperkalaemia. Overall, use of MRA was associated with a higher risk ratio (1.76, 95% CI: 1.20 - 2.57, p=0.004) of hyperkalaemia with low heterogeneity ($\chi^2$=13.73, p=0.8; $I^2$=0%). Neither the exclusion of crossover studies (risk ratio 1.77, 95% CI: 1.19, 2.64, p=0.005; $\chi^2$=10.89, p=0.7; $I^2$=0%), nor exclusion of studies without concomitant ACEi and/or ARB (risk ratio 1.76, 95% CI: 1.18, 2.60, p=0.005: $\chi^2$=13.62, p=0.8; $I^2$=0%) materially affected the result. Both spironolactone (risk ratio 1.97, 95% CI: 1.29, 3.00, p=0.002; $\chi^2$=10.82, p=0.8; $I^2$=0%) and eplerenone (risk ratio 1.97, 95% CI: 1.29, 3.00, p=0.002; $\chi^2$=2.70, p=0.4; $I^2$=0%) were associated with increased risk of hyperkalaemic events.




*Abbreviations: MRA: mineralocorticoid receptor antagonist; CI: confidence interval; IV: inverse variance.*

Figure 3-4: Effect of mineralocorticoid receptor antagonists on serum potassium.

### 3.3.9 End of Treatment Serum Creatinine and Glomerular Filtration Rate

Seventeen studies (827 patients) reported change in serum creatinine. Overall, there was no significant change in serum creatinine (0.04, 95% CI: -0.03, 0.11 mg/dl, p=0.3; Figure 3-5) with the use of MRAs. Exclusion of seven crossover studies made no appreciable difference to the result (0.02, 95% CI: -0.09, 0.13 mg/dl; p=0.7), although there was moderate heterogeneity ($\chi^2$=20.82, p=0.7, $I^2$=52%). Fourteen studies used spironolactone (665 patients) and three (162 patients) used eplerenone with neither agent affecting serum creatinine (0.04, 95% CI: -0.04, 0.12 mg/dl; p=0.1 and 0.04, 95% CI: -0.15, 0.23mg/dl; p=0.7, respectively). Only two studies did not allow concomitant use of an ACEi and/or ARB. Excluding these two studies did not alter the result (0.02, 95% CI: -0.05, 0.09; p=0.6).

Twenty-one studies (1,217 patients) reported changes in GFR. Overall, there was no significant change in the pooled estimate (0.03, 95% CI: -0.08, 0.14 ml/min/1.73$m^2$) with low heterogeneity ($\chi^2$=15.05, p=0.8, $I^2$=0%; Figure 3-5). As for serum creatinine, sub-analyses, excluding crossover studies and studies not allowing concomitant use of ACEi and/or ARB, as well as separate analyses for spironolactone or eplerenone, did not significantly affect the result. Data for doubling of serum creatinine and incidence of ESRD was not extractable in a format required for analysis or not reported in the included studies.

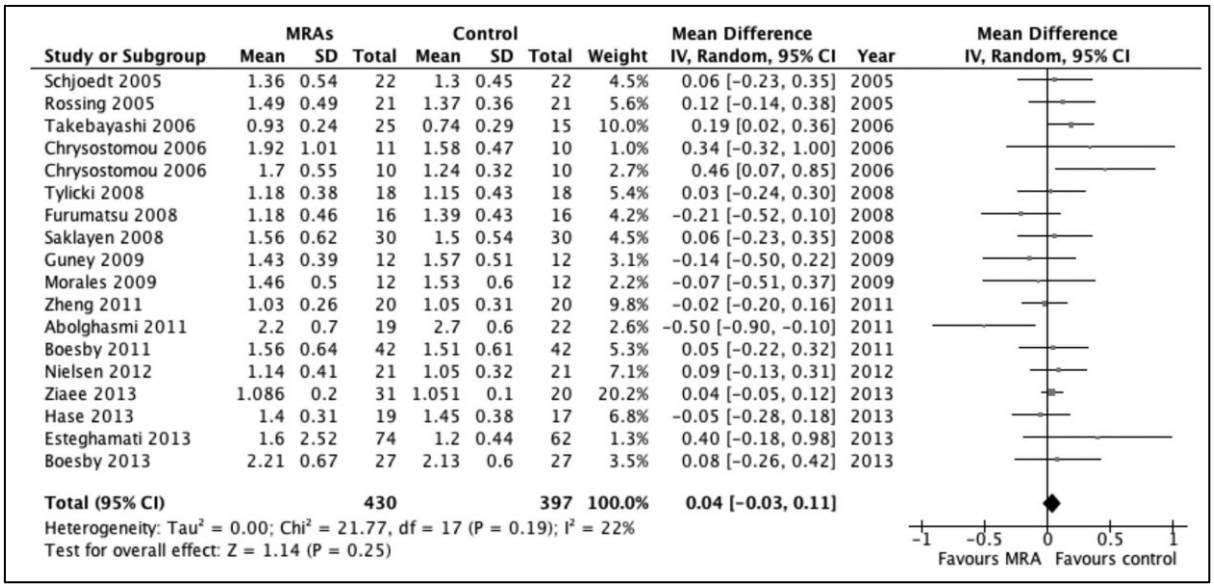



Figure 3-5: Effect of mineralocorticoid receptor antagonist on serum creatinine.

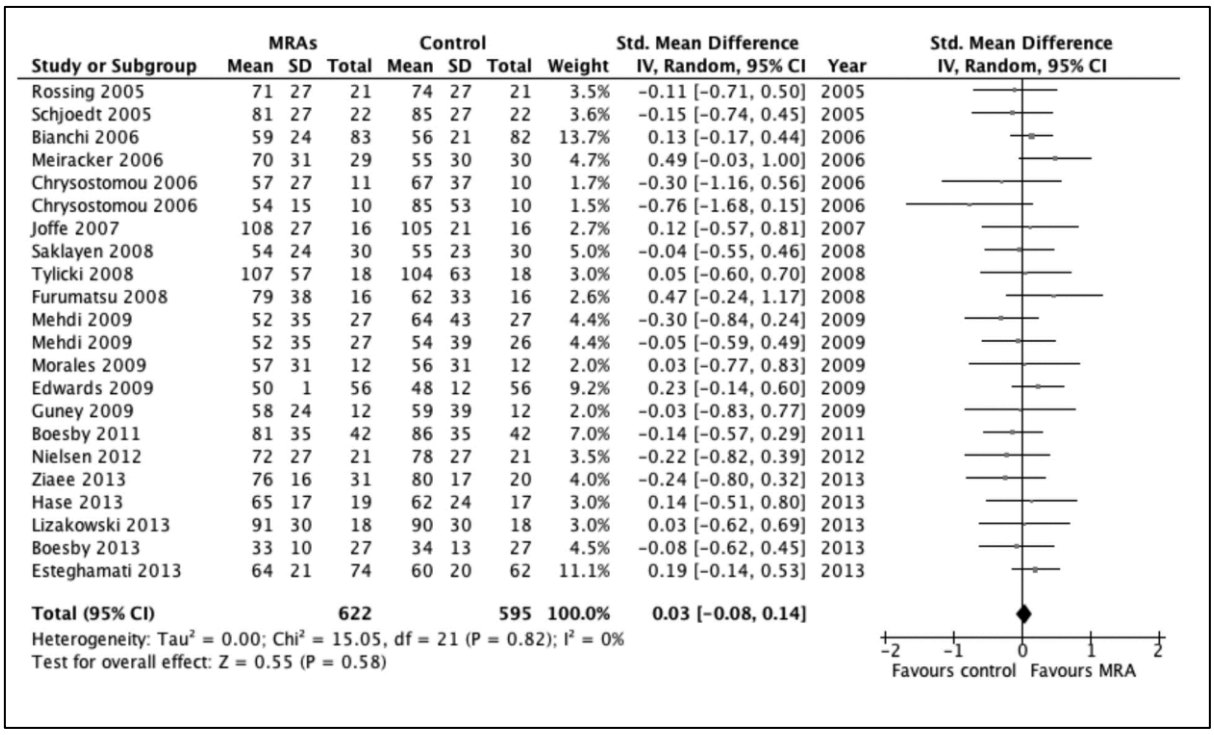



Figure 3-6: Effect of mineralocorticoid receptor antagonist on glomerular filtration rate

### 3.3.10 Cardiovascular Morbidity and Mortality Outcomes

Mortality outcome was reported in three studies, all of which included patients on dialysis only (375, 376, 379). The study durations ranged from six months to two years and included 100 patients. There were six deaths in the placebo arm and three in the MRA arm.

Short-term CV morbidity data was available in two RCTs (367, 375). In a RCT of 81 patients with DM, the hospitalisation rates for CV events were not different for spironolactone, losartan or placebo (367). In contrast, in a RCT study of 16 haemodialysis patients with heart failure, there was a significantly higher number of CV-related hospitalisation events due to ischaemic heart disease and decompensated congestive heart failure in the placebo than the spironolactone arm (12 vs. 2 events, $p>0.01$) (375).

### 3.3.11 Other Adverse Events

Very few studies reported adverse events with any consistency. In all of the studies included, only nine reported breast tenderness/gynaecomastia with a further two reporting them as a cause for study withdrawal. In total, only ten cases of gynecomastia/breast tenderness were reported.

## 3.4 **Discussion**

Our study shows that MRAs potentially improve multiple surrogate markers of CV disease although these studies were relatively few and most included low number of patients. The majority of the endpoints studied are, to a greater or lesser extent, BP dependent and perhaps one of the more important findings from this analysis is that of a significant reduction in SBP and DBP with MRAs even when already treated with an ACEi and/or ARB. Indeed, control

of hypertension is arguably the most important intervention for reducing the increased risk of CV disease and to slow progression to later stages of CKD. Two other important endpoints with prognostic significance, arterial stiffness and LV mass, are causatively influenced by BP (58). Indeed a positive effect on arterial stiffness was only observed in association with BP reduction in one study (140), a finding not replicated in another without any effect on BP (357). Given that MRA use is associated with a significantly increased risk of hyperkalaemia, it remains to be seen whether the use of other "safer" antihypertensive agents, producing the same degree of BP reduction would achieve the same effects. No studies have been powered to examine the impact of MRA on CV morbidity and mortality or indeed any other patient-centred endpoints.

Inhibition of the RAAS with either ACEi or ARB in patients with CKD reduces the rate of deterioration of renal function and the increased CV risk associated with this condition (227). While treatment with MRA might be thought to be of limited efficacy in patients on ACEi or ARB therapy, detailed study of patients on this treatment revealed that in many cases use of ACEi and ARB decreased levels of circulating aldosterone only for a period of weeks (240). In 10-50% of patients, circulating aldosterone concentrations returned to pre-treatment levels, a phenomenon termed aldosterone breakthrough (240). There are reports that patients who demonstrated aldosterone breakthrough had a worse prognosis than those who did not (240). It has been suggested that the use of MRA in this context would be beneficial, especially in the context of renal impairment, and there are many animal and human studies to support this (227).

A further important and not unexpected finding of this analysis was that there was a significant increase in serum potassium concentrations and a significant increase in the risk of hyperkalaemia. In general, there were no data available to examine the influence of baseline renal function on any of these parameters, as has been previously described in robustly conducted meta-analyses examining the actions of MRAs on proteinuria (245, 246). On theoretical grounds, there is reason to believe that hyperkalaemia might be more prevalent in patients with lower GFR values and it is important to note that the actions and safety of MRA in patients with GFR below 30 ml/min/1.73m$^2$ have not been examined in significant numbers of patients. Also, other potential adverse effects of MRA such as gynecomastia have been poorly reported and are likely to underestimate the true incidence. Reduction in proteinuria, a recognised association with CV risk, was the commonest end-point of the studies examined and MRAs are effective at lowering proteinuria (245, 246). However, studies of agents that reduce proteinuria have not always produced concomitant reductions in mortality (382).

Our study has a number of strengths and limitations. We followed current guidelines and identified a large number of studies. The major limitation is the lack of long-term studies on mortality and CV events. The majority of the studies included enrolled few patients and were powered to observe differences in surrogate end-points, mainly reduction in proteinuria. Most studies did not adequately report study methods to assess trial quality. Consistent with other reviews we were also unable to perform separate analyses based on baseline renal function, as data stratified by renal function were unavailable from all the studies (245, 246).

Long-term studies analysing the effect of MRAs on CV events and mortality are warranted. Studies should also examine whether the actions of MRAs are independent of BP reduction

ideally by using a control drug resulting in equal effects on BP. Furthermore, these studies should analyse the efficacy of MRAs in patients who exhibit aldosterone breakthrough, versus those who do not as the beneficial or adverse effects might be different between these two groups. Other factors that could potentially affect response, such as ethnicity (383), level of kidney function, dialysis and transplant status need examining.

In summary, the current evidence does not yet support recommending treatment with MRA for patients with CKD to lower their CV risk. Nevertheless, our increasing understanding of the myriad adverse effects of aldosterone in CKD patients clearly justifies further study of the potential benefits and risks of MRAs drugs in these patients.

## 3.5 **Update on Recent Published Literature**

A repeat electronic search on MEDLINE and EMBASE databases were performed according to the search strategies outlined in the systematic review protocol (Appendix 4-1) on the 29th July 2015. The search identified eight relevant studies which have been published since the previous search (in September 2013) and were not included in the systematic review. Three were on patients with diabetic nephropathy, one on hypertensive population with albuminuria, one on live-kidney transplant recipient, one on peritoneal dialysis population and two on haemodialysis population. These studies were reviewed and their findings are summarised in Table 3-2.

Overall, the recent studies of patients with diabetic nephropathy (384-386) or hypertensive nephropathy (387) continued to demonstrate the beneficial effect of MRAs in albuminuria reduction when compared to diuretics and placebo. Its use was however associated with

increased serum potassium. These findings are in agreement with the results of the systematic review. In a study of 20 live-kidney transplant recipients, Ojeda-Cervantes et al showed that the use of low-dose spironolactone 1-day pre- and 3-days post-transplantation significantly reduced the oxidative stress as assessed by the urinary hydrogen peroxide excretion although there was no difference in renal function or reduction in tubular injury biomarkers (388). Whilst a small study of chronic haemodialysis population without heart failure found that although there was no change in LV dimension or mass over 4 months with the use of spironolactone 25mg daily, it did improve BP, endothelial function and cardiac autonomic status (as assessed by heart rate variability) when compared to placebo (389). In contrast, an RCT of 158 patients on peritoneal dialysis demonstrated statistically significant improvement of the rate of change in both the LV mass index and ejection fraction after 2 years of treatment with low-dose spironolactone or eplerenone when compared to placebo. Encouragingly, there was no serious hyperkalaemia reported during the study (390).

The DOHAS study represented the first RCT examining the effect of MRA on long-term hard-endpoint as primary outcome amongst patients on maintenance haemodialysis (391). This open-label, multicentre Japanese study of 309 patients on haemodialysis reported a statistically significant reduction of death from cerebrovascular/cardiovascular events (CCV) or hospitalisation for CCV (adjusted HR: 0.355, 95% CI: 0.173-0.832, p=0.016) and all-cause mortality (adjusted HR: 0.335, 95% CI: 0.162-0.693, p=0.003) at 3 years after adjusted for sex, duration of dialysis and cardiothoracic ratio amongst those who received spironolactone 25mg daily compared to those without (391). During the study, gynaecomastia or breast pain was reported in 10% of the treatment group and only 2% of the patients discontinued with spironolactone treatment due to hyperkalaemia (391).

To date, the majority of studies of MRAs in CKD population continued to focus on its effect on short-term surrogate markers instead of long-term renal, CV or survival outcomes. Conversely, the success of DOHAS study was encouraging, not least for the haemodialysis population, but also for the nephrology field as a whole. The next few years are likely to see exciting advances especially with the development of aldosterone synthase inhibitors (392) and more cardiac selective MRA (393). With large definitive RCTs, BARACK-D (Benefits of Aldosterone Receptor Antagonism in Chronic Kidney Disease) and ALCHEMIST (ALdosterone Antagonist Chronic HEModialysis Interventional Survival Trial) studies which aim to test the effect of spironolactone on CV morbidity and mortality in patients with stage 3b CKD and patients on haemodialysis, respectively, currently underway; their findings are eagerly anticipated. For now, the concept of MRA being a "renal aspirin" (349) will have to wait.

Table 3-2: Characteristics of the populations and interventions of the additional trials which were published since September 2013.

| Study | Type of study | Study population | Intervention(s) | Also on ACEi/ ARB | Study duration | Outcomes measured | Summary of findings |
|---|---|---|---|---|---|---|---|
| Ojeda-Cervantes et al, 2013 (388) | RCT, double-blinded, parallel. | 20 Live-kidney transplant recipients | Spironolactone 25mg given 1 day before and 3 day post-transplantation vs placebo | no | 5 days | Renal function, urinary KIM-1, IL-18, HSP-72, hydrogen peroxide levels | Spironolactone significantly reduced urinary hydrogen peroxide levels. There was no difference in renal function or reduction in tubular injury biomarkers between the groups. |
| Matsumoto et al, 2014 (391) | RCT, open-label, multicentre, parellel | 309 oligo-anuric patients on haemodialysis | Spironolactone 25mg/day vs none | Yes (43% vs 41%) | 3 years | Composite of death or hospitalization from CCV events, all-cause mortality | Primary composite outcome (HR 0.355, 95% CI: 0.173-0.832) and all cause-mortality (HR 0.355, 95% CI: 0.162-0.693) were reduced in the spironolactone group after adjustment.<br><br>Gynaecomastia or breast pain was reported in 10% of treatment group. Serum $K^+$ >6.5 mmol/L required discontinuation of treatment occurred in 2% of treatment group. |
| Flevari et al, 2013 (389) | Placebo-controlled, sequential trial | 14 patients on maintenance haemodialysis without heart failure | Spironolactone 25mg thrice weekly vs placebo | | 4 months | Forearm reactive hyperemic during after venous occlusion plethysmography, heart rate variability, BP, echocardiographic and laboratory data. | Improvement in endothelial function ($p<0.05$), heart rate variability ($p<0.05$) and blood pressure control ($p<0.05$) in spironolactone group compared with control. No change in LV dimension or mass between groups. |
| Ito et al, 2013 (390) | RCT, open-label, multicentre, parellel | 158 patients on peritoneal dialysis with NYHA I or II | Spironolactone 25mg/day or Eplerenone 50mg/day vs none | yes | 2 years | LVMI and LVEF, residual renal function, peritoneal membrane function. | Improvement in rate of change in LVMI ($p=0.01$) and LVEF ($p=0.02$) in spironolactone group compared with control. There was no difference in secondary outcomes between the groups. |

| Study | Type of study | Study population | Intervention(s) | Also on ACEi/ ARB | Study duration | Outcomes measured | Summary of findings |
|---|---|---|---|---|---|---|---|
| Momeni et al, 2015 (384) | RCT, double-blinded, parellel | 60 patients with diabetic nephropathy, proteinuria >150mg/day, CG GFR >30 mL/min | (1)spironolactone 50mg/day + placebo; (2)spironolactone 50mg/day + hydrochlorothiazide 25mg /day; (3)hydrochlorothiazide 25mg /day + placebo | Yes | 3 months | 24-hour urine protein, serum potassium, renal function | Reduction of proteinuria in group 1 & 2 compared to group 3 ($p<0.001$).<br><br>Increase serum K+ of .026 mEq/L ($p=0.002$) in group 1, but not in group 2 or 3. There was no difference in GFR amongst the groups. |
| Makhlough et al, 2014 (385) | RCT, double-blinded, parellel | 60 patients with Type II diabetic and microalbuminuria | Spironolactone 25mg/day + placebo vs Spironolactone 25mg/day + losartan 12.5mg BD | No | 3 months | Reduction of albuminuria > 50% (treatment success rate), BP, serum potassium and renal function. | No statistical significant difference in treatment success rate ($p=0.4$), serum potassium ($p=0.08$), BP ($p=0.6$) and serum creatinine ($p=0.4$) between the groups. |
| Ando, et al, 2014 (387) | RCT, double-blinded, parellel | 336 Patients with hypertension with uACR=30-599 mg/g and eGFR > 50mL/min/1.73m$^2$ ) | Eplerenone 50 mg/day vs placebo | Yes | 1 year | Percent change in uACR in the first morning void urine at week 52 from baseline | Significant reduction of uACR in eplerenone group compared to placebo (absolute mean difference -276%, $p=0.022$). |
| Van Buren et al, 2014 (386) | RCT, double-blinded, parellel | 80 patients with diabetic nephropathy | (1) spironolactone 25mg/day; (2) losartan 100mg/day; (3) placebo | Yes. Lisinopril 80mg/day | 48 weeks | Serum potassium, aldosterone, 24 hour urine sodium, potassium and creatinine | Spironolactone raised serum potassium more than losartan, despite similar renal sodium and potassium excretion. |

*Abbreviations: ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BD, twice daily; BP, blood pressure; CCV, cerebrovascular and cardiovascular; CI, confidence interval; HR, hazard ratio; HSP, heat shock protein; IL, interleukin; $K^+$, potassium; KIM, kidney injury molecule; LVEF, left ventricular ejection function; LVMI, left ventricular mass index; NYHA, New York Heart Association; uACR, urine albumin:creatinine ratio.*

# CHAPTER 4 SPIRONOLACTONE TO PREVENT CARDIOVASCULAR EVENTS IN EARLY STAGE CHRONIC KIDNEY DISEASE (STOP-CKD) STUDY: MIXED METHODS APPROACH

## 4.1 Introduction

To date, systematic reviews have convincingly concluded the proteinuria reduction effect of the use of MRAs in additional to ACEi or ARB therapy in patients with CKD (244-246). Nonetheless, its effects on the long-term CV and survival outcomes in this population remain undetermined and clearly warrant further investigations (see Chapter 3).

CKD is associated with increased arterial stiffness even in the early stages and this is thought to be a key mediator in the pathophysiology of its increased CV risk (394). Notably, many of these abnormalities are evident even in patients with early stages of CKD (65, 66) despite satisfactory BP control (67). In a recent randomised, double-blinded, placebo-controlled trial of 112 patients with stage 2-3 CKD in secondary care setting (CRIB II study), Edwards et al demonstrated the significant beneficial effects of low-dose, non-selective MRA (spironolactone 25mg/day) in reducing LV mass and improving arterial stiffness, as measured by cfPWV (140, 248, 249). These promising, though, preliminary findings from CRIB II study suggested a potential under-utilisation of this well-established medication. In addition, it also provided a strong basis for further research to examine the effects of MRAs in CV and survival outcomes in the CKD population.

Patients with stage 3 CKD (eGFR 30-59 ml/min/1.73m$^2$) represent the largest group amongst the CKD population and they accounts for approximately 3.7% of the total U.K. adult population (35). Patients with such moderate degree of CKD have been shown to have much greater risk of dying from adverse CV events than progressing to ESRD (61). While majority of the CKD studies were conducted in secondary care, patients with stage 3 CKD in the U.K. are in fact mostly managed in the primary care setting (395, 396) and are often older with less well-defined renal phenotypes than the patients included in the hospital-based study. In addition, there were often concerns amongst the general practitioners regarding the risk of hyperkalaemia and renal dysfunction associated with the use of MRAs in the CKD population (245).

A pilot study to examine if desirable intermediate CV end-points changes can equally be achieved via the use of low-dose spironolactone in the primary care CKD cohort and to test the feasibility of a large and appropriately powered definitive trial is clearly warranted. The STOP-CKD study was therefore conceived and designed out of such needs. It was a mix-method study, involving both a RCT (quantitative arm) as well as an interview study (qualitative arm). Its primary objective was to determine the effect of spironolactone on arterial stiffness in non-diabetic patients with stage 3 CKD managed in primary care. In addition, the study also aimed to determine the safety of spironolactone in stage 3 CKD stage in the community; assess the effect of low-dose spironolactone on BP and albuminuria in stage 3 CKD and qualitatively explore patients' and healthcare professionals' attitudes towards CKD, research in CKD and potential barriers to the use of spironolactone in CKD in a community setting (Table 4-1).

This chapter focuses on the methodology of the quantitative STOP-CKD RCT. The methods and results of the qualitative STOP-CKD interview are detailed in Chapter 6 and 7.

## 4.2 **Hypothesis of STOP-CKD Study**

Low-dose spironolactone decreases arterial stiffness in patients with stage 3 CKD. The objectives of the study are detailed in Table 4-1.

Table 4-1: STOP-CKD study objectives

| | | |
|---|---|---|
| Pilot study | | To determine the recruitment rate and feasibility of the study. |
| Quantitative arm | Primary | To determine the effect of low-dose spironolactone on arterial stiffness in patients with stage 3 CKD. |
| | Secondary | To determine the safety of spironolactone in patients with stage 3 CKD in primary care setting, in regards to the incidence of hyperkalaemia, worsened renal function and other adverse events. |
| | | To assess the effect of spironolactone on blood pressure and albuminuria. |
| | | To assess the effect of spironolactone on pulse wave characteristics. |
| Qualitative arm | | To examine patients' and healthcare professionals' attitudes towards CKD and research in CKD in the community setting. |
| | | Explore patients' and healthcare professionals' attitudes towards the use of spironolactone in CKD in a community setting and the potential barriers which might exist to its use. |
| | | *(The methods and results of this qualitative study were presented in Chapter 6 & 7)* |

*Abbreviation: CKD, chronic kidney disease.*

## 4.3 **Quantitative Study Design**

The quantitative arm of STOP-CKD study was a multicentre, prospective, randomised, placebo-controlled, double-blinded pilot trial in patients with stage 3 CKD. Patients registered

in participating primary care practices within South Birmingham, England were screened with a view to recruiting 240 eligible participants. Potential participants were identified by searching computerised primary care clinical records for patients with a latest eGFR value of 30 to 59 ml/min per 1.73 $m^2$ in the preceding 12 months. The GFR was estimated by the four-variable MDRD formula with serum creatinine recalibrated to be traceable to an isotope-derived mass spectroscopy method (24). The details of this computerised search are available in Appendix 4-1.

Decision was made to perform the search on patients' eGFR records instead of practices' coded CKD diagnosis as a recent retrospective cohort study highlighted the issue with identification and accurate classification of CKD in primary care (35). Approximately 1% of the population were reported not to be on practice CKD register though they fulfilled the biochemical criteria for CKD (un-coded CKD) and 2% were erroneously included on the register when they did not fulfil the biochemical criteria (mis-coded CKD) (35). Therefore, short-listing patients according to practices' coded CKD would not only result in overlooking large pool of potentially eligible patients but would also incorrectly inviting many who were in fact not suitable for the study and therefore, affecting the efficiency of the research screening process. By searching using previous eGFR record, the study was able to capture a larger pool of potential participants. As eGFR was rechecked during research screening visit, the diagnosis of CKD would then be confirmed or refuted and this information was also used to feed back to the practice to improve their coding of CKD diagnosis. Nevertheless, the research team was also aware of the risk of inviting patients who were not aware of their potential CKD diagnosis or might not in fact have CKD after the confirmatory eGFR test on the screening visit. Therefore, the patients' research invitation letter had been carefully

phrased in order to minimise patients' anxiety towards this potentially unconfirmed diagnosis. The invitation letter approved by the ethics committee stated that patients had been invited for STOP-CKD study as they 'have had blood tests in the past indicating they may have a lowered kidney function' (Appendix 4-2).

The research invitation letters (Appendix 4-2) as well as patient information sheets (Appendix 4-3) were sent out to all potentially eligible patients. They were invited to attend a screening visit with the research team at their own general practice, where the study was explained further. The research team obtained written consent from all willing participants prior to their enrolment into the study (Appendix 4-4). Following the screening visit, all recruited eligible, consenting participants were randomised to receive either placebo or spironolactone 25 mg once daily orally for an intended period of 40 weeks (Figure 4-1). The cfPWV was measured using a Vicorder system (Skidmore, Bristol, UK) at baseline and at end-of-study to detect any change in arterial stiffness (309). Outcomes were analysed using an intention-to-treat analysis.

Ethical approval has been received from the National Research Ethics Service West Midlands Coventry and Warwickshire (Reference No 12/WM/0168) and clinical trial authorisation has been granted by the Medicine and Healthcare Products Regulatory Agency (MHRA) (Reference No 21761/0274/001-0001). The sponsor, investigators, trial steering committee (TSC), data management committee (DMC), coordinating centre, recruiting sites, all members of the study team and all trial participants were informed of the modifications. The study was coordinated by the Primary Care Clinical Research & Trials Unit (PC-CRTU), which has been fully accredited by the National Institute for Health Research (NIHR) as a trials unit at

the University of Birmingham according to the current guidelines for Good Clinical Practice. The study was monitored to confirm compliance with the protocol and the protection of patients' rights, as detailed in the Declaration of Helsinki. The inclusion and exclusion criteria are detailed in Table 4-2.

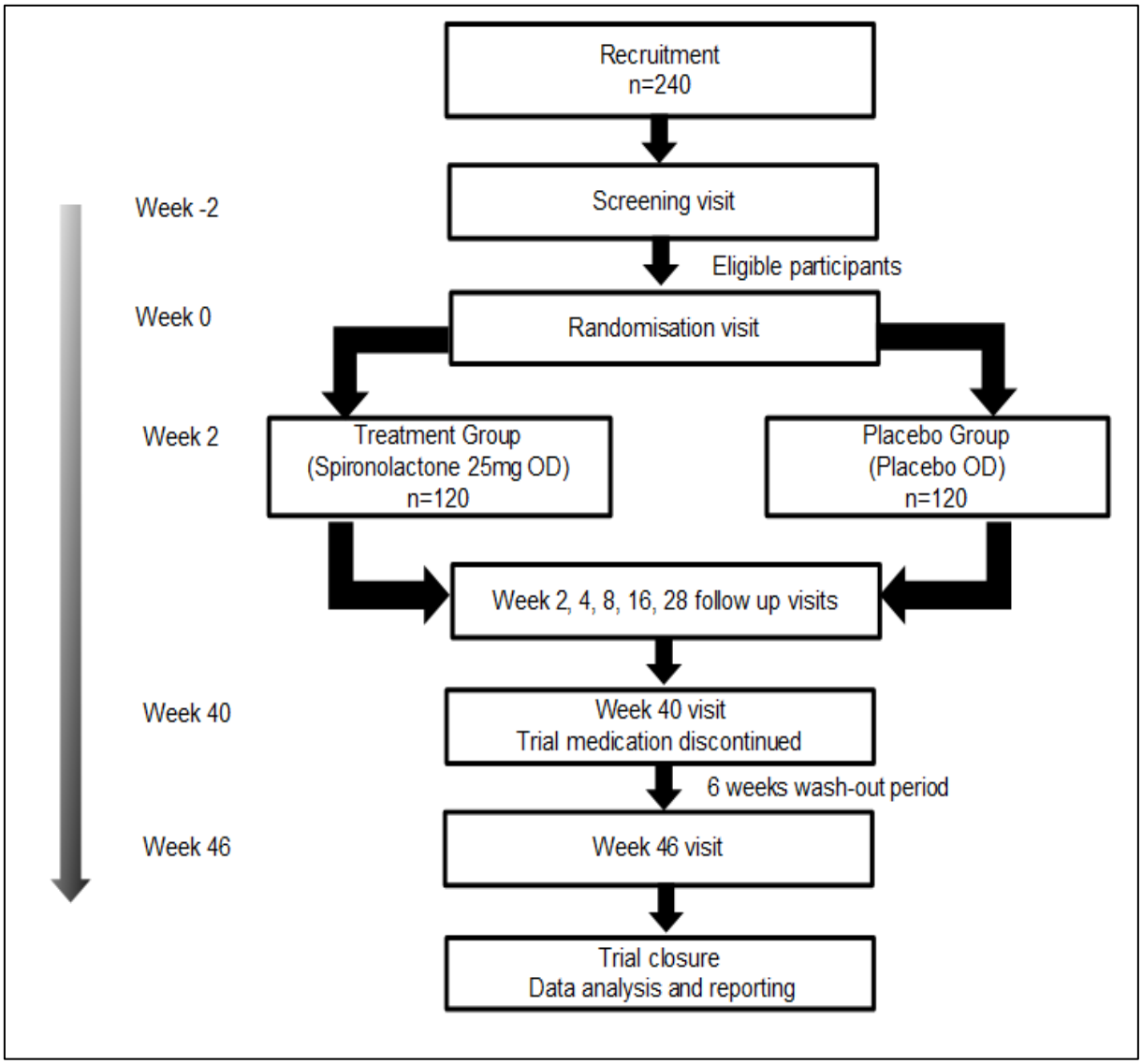
Patients with diabetes mellitus are excluded in this study for a number of reasons. The pathophysiology of arterial stiffness might be different, with a greater importance of advanced glycation end-products, for example (58). Furthermore, vascular calcification is more common and thus arterial stiffness may be less likely to improve with spironolactone (58). Hyperkalaemia is more common in patients with CKD and diabetes than without; and this may be markedly worsened by spironolactone. Diabetes would be expected to affect 20-30% of a community sample of CKD, and hence would form a large subgroup within the trial. Thus, although diabetes is an important issue in CKD, this would be best explored in a separate study concentrating on diabetes rather than affecting the risk: benefit ratio of the proposed study in terms of reduced chance of outcome and a greater number of adverse events than expected.

Table 4-2: Inclusion and exclusion criteria of STOP-CKD study

| **Inclusion criteria** |
|---|
| Age over 18 years |
| Diagnosis of CKD Stage 3 (MDRD eGFR 30-59 ml/min/1.73m$^2$) |
| **Exclusion criteria** |
| Diabetes Mellitus |
| Terminal disease or considered otherwise unsuitable by GP |
| Clinical diagnosis of chronic heart failure |
| Atrial fibrillation |
| Alcohol or drug abuse |
| Inability to comply with trial medication and follow-up |
| Documented previous hyperkalaemia or intolerance of spironolactone |
| Documented Addisonian crisis or taking fludrocortisone |
| Severe hypertension: BP ≥ 180/110 mmHg |
| Systolic BP < 120 mmHg |
| Recent acute kidney injury or hospital admission (within previous 6 weeks) |
| Chronic diarrhoea |
| Urine albumin:creatinine ratio (uACR) ≥ 70 mg/mmol |
| Serum potassium ≥ 5 mEq/l on screening visit |
| Concomitant co-trimoxazole medication |
| Concomitant ACEI and ARB medication (dual-blockade) |
| Concomitant lithium medication |
| Concomitant warfarin medication |
| Pregnancy |
| Breastfeeding |
| Planned major surgical intervention within 46 weeks of recruitment |

### 4.3.1 Study Procedure

The study timeline and schedule of follow-ups and assessments are summarised in Figure 4-1 and Table 4-3.




*Abbreviation: OD, once daily.*

Figure 4-1: Study timeline of STOP-CKD RCT

Table 4-3: Flowchart of assessment for STOP-CKD RCT

| | | Treatment | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Visit (week)** | **Screening** | **Randomisation** | **2** | **4** | **8** | **16** | **28** | **40** | **46** |
| Valid informed consent gained | √ | √ | | | | | | | |
| Full demographic details | √ | | | | | | | | |
| Relevant medical history taken | √ | √ | | | | | | | |
| Concomitant medications | √ | √ | √ | √ | √ | √ | √ | | |
| Anthropometric measurements | | √ | | | | | | | |
| Blood pressure measurement | √ | √ | √ | √ | √ | √ | √ | √ | √ |
| Pulse wave velocity and pulse waveform analysis measurement | | √ | | | | | | √ | √ |
| Haematological & Full biochemical profile | √ | | √ | | | | | √ | √ |
| Renal profile | | | | √ | √ | √ | √ | | |
| Urine albumin:creatinine ratio | √ | | | | | | | √ | √ |
| EQ5D-5L Questionnaire | | √ | | | | | | √ | |
| Medication Monitoring Questionnaire | | √ | √ | √ | √ | √ | √ | √ | √ |

*Abbreviation: EQ5D-5L, European quality of life-5 dimensions*

### 4.3.2 Screening Visit

All consenting participants attended screening visit during which the following were carried out: (i) completion of a questionnaire regarding demographic details, relevant medical history and concomitant medication; (ii) non-invasive BP measurement using an automated BpTRU machine (BPM-100, BpTRU™) (see section 4.3.5.1) (308); (iii) blood and urine sampling. Estimated GFR on this screening visit confirmed the diagnosis of stage 3 CKD (two MDRD eGFR measurements of 30 to 59 ml/min per 1.73 $m^2$ at least 90 days apart). A urine test was used to exclude patients who have a uACR > 70 mg/mmol. Participants with BP >140/90 mmHg and a uACR of 30 to 69 mg/mmol but not receiving either ACEi or ARB were referred to their GP to be considered for ACEi or ARB treatment. They were re-invited to the screening visit after at least 6 weeks treatment with ACEi or ARB.

### 4.3.3 Randomisation Visit

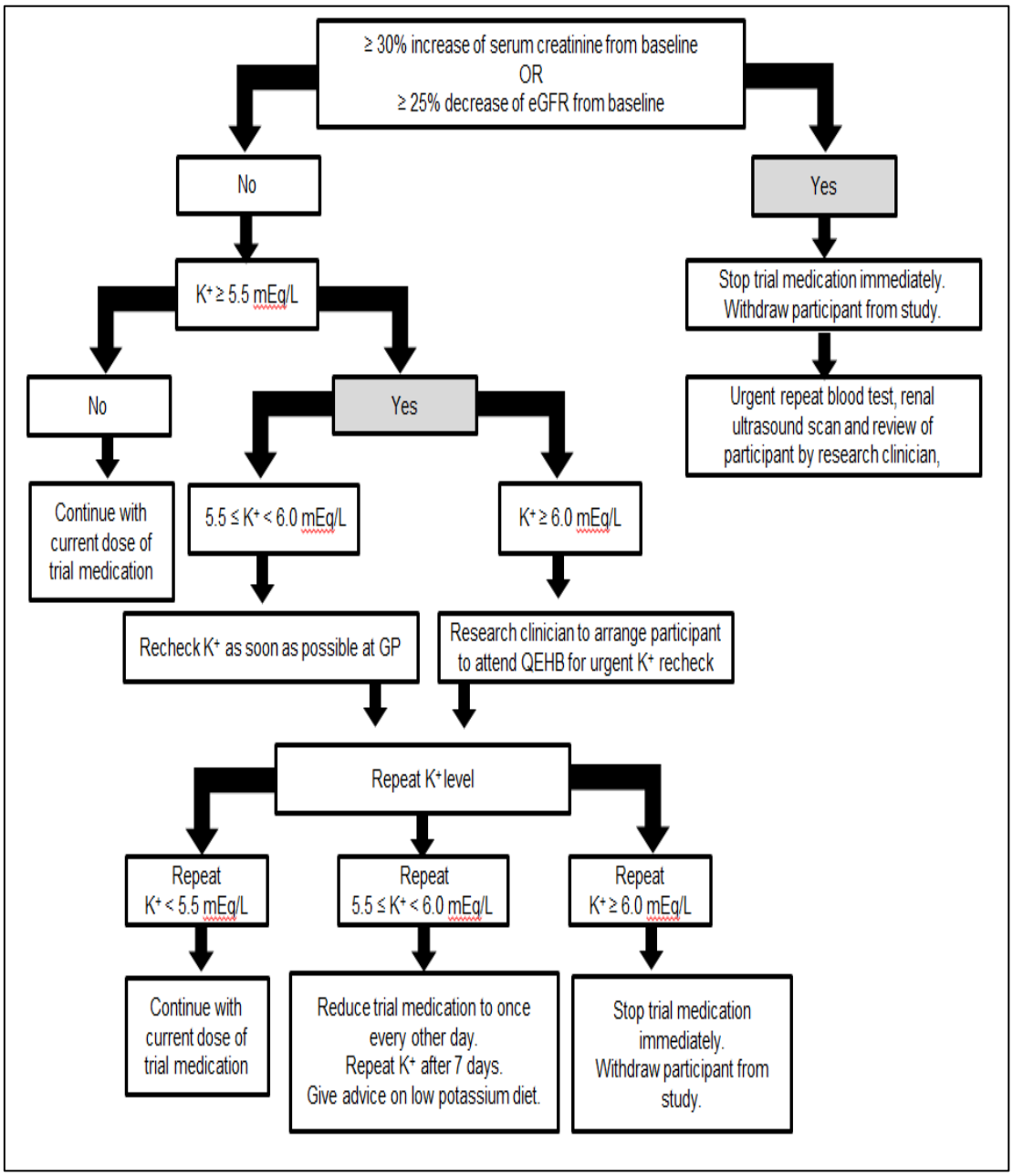
Eligible patients were invited back no later than two weeks after their initial visit to attend a randomisation clinic. Informed consent was sought again before randomisation to commence trial medication (Appendix 4-5). Consenting participants underwent the following assessments: (i) EQ5D-5 L (European Quality of Life, 5 Dimensions, 5 Levels) (397) and medication monitoring questionnaires (Appendix 4-6); (ii) anthropometric measurements, which included height, weight and neck, waist and hip circumferences ; (iii) BP measurement; (iv) cfPWV measurement and PWA (see section 4.3.5.1.2). All participants were randomised to receive either inactive placebo or spironolactone 25 mg once daily orally.

### 4.3.4 Follow-up Visits

Following randomisation, all participants attended follow-up visits at weeks 2, 4, 8, 16 and 28. The medication monitoring questionnaires were filled in and brachial BP measurements as well as blood samples to monitor serum electrolytes and renal function were taken at each visit. Abnormal BP readings were managed according to STOP-CKD working instruction (Appendix 4-7). Participants with a persistently elevated BP of more than 150/90 mmHg were referred to their GP for BP management according to the NICE guidelines (398) . Participants with hyperkalaemia or renal function deterioration during the follow-up visits were managed according to the study protocol (Figure 4-2).

All measurements performed at the screening and randomised visits were planned to be at 40 weeks after the randomisation, marking the end of the treatment phase. All participants discontinued the trial medication and adherence was assessed via pill count. After a wash-out

period of six weeks, all participants were planned to have final follow-up visits (week 46 visit) whereby all measurements performed at the week 40 visit were repeated.




*Abbreviations: eGFR, estimated glomerular filtration rate; K+, serum potassium concentration.*

Figure 4-2: Study flowchart on management of renal dysfunction and hyperkalaemia in the STOP-CKD trial.

### 4.3.5 Study Assessments

#### *4.3.5.1 Blood Pressure Measurement*

Blood pressure was measured using the BpTRU™ BPM-100 automated BP monitor (308) (Appendix 4-8). During the screening visit, six serial sitting BP measurements were taken simultaneously on both arms, to identify which arm to use for BP monitoring for all future visits. These six BP measurements were performed via the automated machine at 1 minute intervals. Each BP reading was recorded. The office mean BP was derived from the mean of the 2nd and 3rd BP readings, whereas the mean BpTRU reading was derived from the mean of the 2nd, 3rd, 4th, 5th and 6th readings. If there was >20 mmHg difference in systolic BP or >10 mmHg difference in diastolic BP on the office meanBP reading between the arms, the arm with the higher reading was selected for all future BP and Vicorder measurements. If not, the non-dominant arm was the selected measured arm. After measurement of sitting BP, postural BP was measured after asking the participant to stand up for 1 minute from sitting position. Postural hypotension is defined as a drop of systolic BP >20 mmHg on standing. Serial sitting BpTRU BP measurements and postural BP was repeated during each follow-up visits and at end-of-study.

#### *4.3.5.2 Carotid-Femoral Pulse Wave Velocity and Pulse Wave Analysis Measurements*

The Vicorder system provides a non-invasive, non-operator-dependent method of obtaining cfPWV and pulse wave characteristics using a volume displacement technique (Appendix 4-9). In comparison to SphygmoCor device, although Vicorder appeared to report lower cfPWV values at higher cfPWV measured by SphygmoCor, it was found to have high repeatability with low within-subject coefficient variation of 2.8% (309). After correction for the distance to the pulse detection point between the devices, Vicorder was reported to have, in general,

good agreement with SphygmoCor in cfPWV measurements (309). Additionally, Pucci et al also demonstrated that the estimated central BP generated by Vicorder device was reliable when calibrated to invasive pressure (310).

Carotid-femoral PWV measurements were obtained by placing a 100-mm-wide BP cuff on the proximal thigh to measure the femoral pulse and a 30-mm-wide partial cuff on the neck at the level of the carotid artery. The aortic path length is defined as the distance between the mid-clavicular point and the middle of the thigh cuff. This length was measured by the operator and input into the Vicorder System. With the participants lying supine at approximately 30° with the head and shoulders supported by a pillow to prevent flexion of the neck, the cuffs each inflated to 60 mmHg and the corresponding oscillometric signal from each cuff was digitally analysed to extract, in real time, the pulse waveforms and pulse transit time from carotid to femoral sites. Subsequently, cfPWV was derived from the measured pulse transit time and aortic path length. Similarly, pulse wave characteristics and analysis was performed by placing the 100-mm-wide BP cuffs on the selected arm and proximal thigh.

$$PWV = K \times Transit\ Time/Distance$$

The cfPWV and PWA measurements were performed on the same side as for BP for each participant after 5 minutes of rest. The cfPWV and PWA measurements were performed in triplicate. The mean value of the three recordings was used for subsequent analysis. Inconsistent values among the three recordings were further examined by a designated senior investigator not involved in taking the measurements, to determine the validity of each measurement. Example of the Vicorder outputs, demonstrating transit time, calculated PWV

and carotid and femoral wave form as well as pulse wave analysis (PWA) are shown in Figure 1-1 and 1-2, respectively.

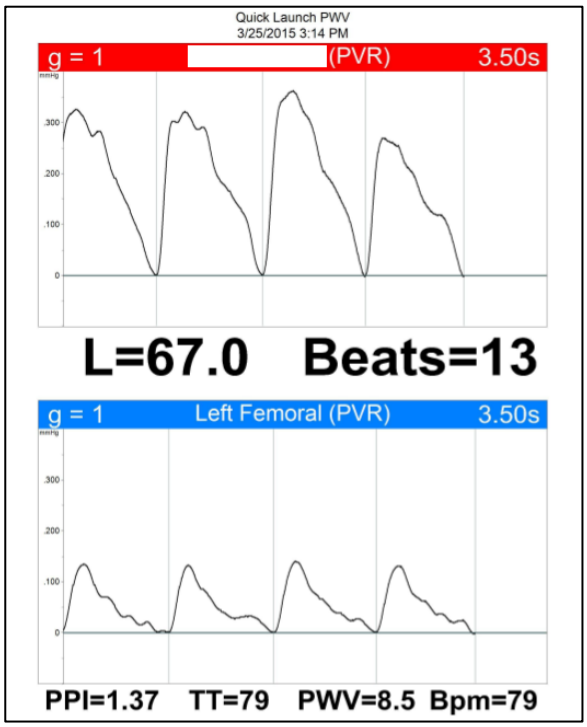



Figure 4-3: An example of the output from the Vicorder device showing carotid and femoral pulse wave (cfPWV), transit time (TT) and the calculated pulse wave velocity (PWV).

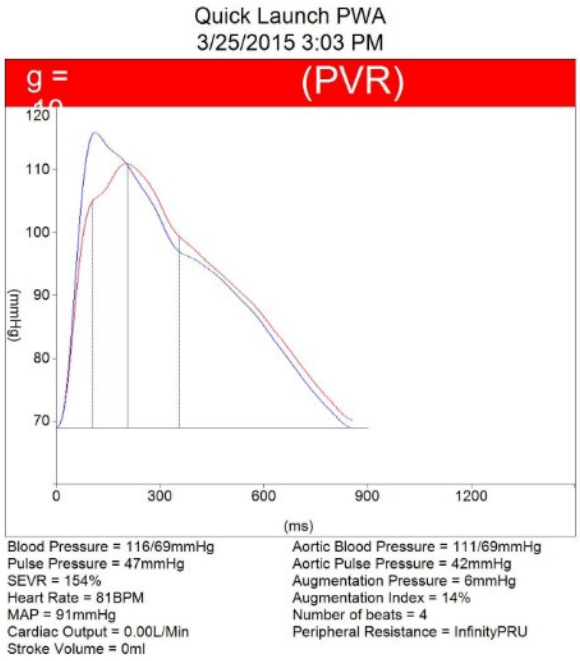



Figure 4-4: An example of the output from the Vicorder device showing an analysis of the arterial pulse waveform (pulse wave analysis: PWA) which includes measurements of heart rate, mean arterial pressure, aortic and brachial blood pressure and pulse pressure, augmentation pressure, augmentation index and sub-endocardial viability ratio (SEVR).

## 4.4 **Randomisation**

Investigators, outcome assessors, data analysts and participants were all blinded to the treatment allocation via the use of an apparently identical inert placebo and a central automated allocation procedure. Participants were stratified by practice location, SBP (above or below 140 mmHg) and urine albuminuria (uACR above or below 30 mg/mmol) and assigned to either active treatment or inactive placebo using a minimization algorithm with a 70:30 weighted-coined approach if there is an imbalance. This randomisation assignment was centrally operated using the PC-CRTU secured web-based randomisation system. A unique five-digit trial medication number, which corresponded to either active or placebo treatment, was generated for each participant randomised.

## 4.5 **Treatment**

The trial medication was supplied by an authorised trial medication manufacturing unit. The placebo medications were made with Swedish Orange Gelatin capsules, size DBAA capsules filled with Cellulose, Microcrystalline with 1% Magnesium Stearate. Whilst the active medications were manufactured via the over-encapsulation of a 25mg Spironolactone tablet in a Swedish Orange Gelatin capsule, size DBAA and back-filled with Cellulose, Microcrystalline with 1% Magnesium Stearate to match the aspect and weight of the placebo capsules. These capsules were further packed into Plastic White HDPE Screw Neck 200ml bottles, each consisting of 100 capsules of either active medication or placebo. The bottles were labelled according to Good Manufacturing Practice Annex 13 Investigational Medicinal Products as per approved label. In addition to the labels, there were small tear-off labels containing unblinded information, either A or B, on the bottles. This information indicated if the bottles contained active or placebo medication.

These packaged trial medications were then delivered to a designated community pharmacy hub. STOP-CKD study delegated the duty of storing and dispensing the trial medication to a large community pharmacy operator. A standard operating procedure (SOP) of such responsibilities were drawn up and agreed between both parties. All pharmacists involved in the dispensing of the STOP-CKD trial medications underwent training from the research team and had read and understood the SOP.

The list which contained all the unique trial medication numbers and their corresponding treatment options (A or B) were sent from the informatics team responsible for the randomisation programme at the PC-CRTU to the designated hub pharmacy. Upon receiving

the STOP-CKD prescription from the research team, pharmacist at the hub pharmacy verified the prescription, matched up the unique trial medication number on the prescription to their identifier (A or B), dispensed the corresponding trial medication bottles and removed the tear-off labels. The trial medication was then delivered to the local community pharmacy closest to the recruiting practice for collection by the participant.

During the 40 weeks treatment, all participants completed the medication monitoring questionnaire at each research visit to record any side effect related to the trial medication and self-report trial medication compliance. In the event when participant's serum potassium concentration was 5.5 to 5.9 mmol/l on repeat samplings, the trial medication was reduced from once daily to once every other day (see Figure 4-2).

## 4.6 **Withdrawal Criteria**

Participants were withdrawn from the trial when they chose not to continue, when their GP considered that continued participation in the trial was inappropriate or when they were no longer eligible according to the withdrawal criteria listed in Table 4-4. Participants who withdrew from the trial were asked if they were willing to attend a final research visit within seven days of stopping the trial medication for blood and urine sampling, BP and Vicorder measurement and completion of the EQ5D-5L (European Quality of Life- 5 dimensions) and medication monitoring questionnaire. Data were collected for an intention-to-treat analysis.

Table 4-4: Withdrawal criteria for STOP-CKD study.

| System | Adverse effect | Actions |
|---|---|---|
| Blood pressure | Hypotension | To withdrawal trial medication if SBP <100 mmHg or postural drop of SBP >20 mmHg. |
| Metabolic | Hyperkalaemia | Serum potassium ≥ 6 mmol/L on repeat sampling. |
| | Hyponatremia | To withdraw trial medication if serum sodium <130 mmol/L on 2 occasions. |
| Renal | Renal Dysfunction | Serum creatinine increment ≥30% or eGFR reduction ≥25% from baseline. |
| Endocrine | *Male*: Gynaecomastia, impotence, diminished libido.<br>*Female*: hirsutism, oligomenorrhoea, amenorrhoea, menorrhagia, breast tenderness | To withdraw trial medication if participant is intolerant of the side effect/effects. |
| Nervous system | Headache | To withdraw trial medication if symptom persists for >1 week. |
| | Confusion, ataxia, drowsiness | To check postural blood pressure and serum sodium level. If postural blood pressure and serum sodium are within normal level, but symptom persist for > 1 week, to withdraw trial medication. |
| | Lethargy | To withdraw trial medication if symptom persists for > 1 week. |
| Dermatologic | Rash | To withdraw trial medication. |
| | Lichen planus, lupus-like syndrome | To withdraw trial medication. |
| Hypersensitivity | Anaphylaxis, contact dermatitis, eosinophilia. | To withdraw trial medication immediately. |
| Gastrointestinal | General abdominal discomfort | To withdraw trial medication if persistent discomfort for > 1 weeks. |
| | Diarrhoea or vomiting | To withdraw trial medication if persistent diarrhoea or vomiting for >3 days. |
| | Gastric/ duodenal ulcer or bleeding | To withdraw trial medication. |
| Haematological | Agranulocytosis | To withdraw trial medication. |
| Hepatic | Hepatotoxicity (ALT > 123 U/L OR bilirubin > 44 μmol/L) | To withdraw trial medication. |
| Oncologic | Animal studies suggested association between spironolactone with benign adenoma of the thyroid and testes, malignant breast tumours, hepatocellular carcinoma and leukemia. | To withdraw trial medication. |

*Abbreviation: ALT: Alanine transferase; SBP: systolic blood pressure*

## 4.7 **Endpoints**

The primary endpoint of the study was the change in cfPWV between baseline and 40 weeks. Secondary endpoints were: (i) change in brachial BP; (ii) change in MDRD eGFR; (iii) change in uACR; (iv) change in pulse waveform characteristics; (v) incidence of hyperkalaemia; (vi) incidence of renal dysfunction (increment of creatinine ≥ 30% or reduction of eGFR ≥ 25% from baseline); (vii) incidence of other adverse events.

## 4.8 **Sample Size Calculation**

In the previous study of the effect of spironolactone, the Chronic Renal Impairment in Birmingham II (CRIB II) study, the standard deviation of the change in cfPWV was 1.0 m/s in the active treatment group and 0.9 m/s in the control group (140). Hence, 100 subjects in each arm will provide 90% power with an $\alpha$ value of 0.05 to demonstrate a difference in change of cfPWV of 0.5 m/s between the active treatment and control groups. We intended to recruit 240 patients to account for an approximate drop-out rate of 20%, which would result in at least 200 patients completing this randomized control trial, with 100 patients in each arm (inactive placebo versus spironolactone).

## 4.9 **Trial Management**

The STOP-CKD study was coordinated by the PC-CRTU at the University of Birmingham according to the current guidelines for Good Clinical Practice. Data entry, coding, security, storage, access and quality assurance were managed according to the PC-CRTU policy. The chief investigator (Dr Charles Ferro) took overall responsibility for the conduct of study. Any delegated or devolved responsibility was documented in a delegation log. An investigators

group met monthly to provide oversight of the developing trial, with more frequent operational meeting of the chief investigator, trial manager and trial team as required.

A TSC was appointed and provided overall supervision for the trial, in particular: trial progress, protocol compliance, patient safety and review of updated information. The TSC included the trial management group, two lay representatives and an independent chair who has expertise relevant to the study (Appendix 4-10). The TSC met every 3 to 6 months, depending on the phase of the study.

An independent DMC for the trial was responsible for the regular monitoring of trial data. The committee consisted of an independent secondary care clinician, an independent academic GP and an independent statistician (Appendix 4-11). The DMC assessed the progress of the trial and gave advice on whether the accumulated data from the trial, together with the results from other relevant trials, justified the continuing recruitment of further patients. The committee met in person or by teleconference prior to the trial commencement and then 3 and 6 months after initiation of the trial. The DMC made confidential recommendations to the TSC as the decision-making committee for the trial (Appendix 4-11).

## 4.10 **Monitoring and Safety Assessments**

Monitoring which was performed according to the PC-CRTU policy was conducted centrally and at each local recruitment sites. Any major problems identified during monitoring were reported to the TSC. All records were maintained in accordance with local regulations and in a manner that ensured security and confidentiality. All adverse events and severe adverse events were recorded and followed up for the duration of the study or until resolution.

Assessment of adverse events was performed by the study investigators. All serious adverse events were graded and reported to the sponsor. Any suspected unexpected serious adverse reactions were reported to the sponsor, ethics committee as well as MHRA.

# CHAPTER 5 SPIRONOLACTONE TO PREVENT CARDIOVASCULAR EVENTS IN EARLY STAGE CHRONIC KIDNEY DISEASE (STOP-CKD) STUDY: QUANTITATIVE OUTCOMES REPORTING

## 5.1 Introduction

The STOP-CKD pilot RCT was conducted as described in the methodology chapter (see Chapter 4). In brief, the aims of this quantitative arm of the study were primarily to determine the recruitment rate and feasibility of the study design as well as examine the effect of low-dose spironolactone on arterial stiffness in patients with stage 3 CKD in primary care. The secondary aims of the RCT included determining the safety of low-dose spironolactone and its effect on BP, albuminuria and pulse wave characteristics in such population. Using the data generated from the STOP-CKD RCT, this chapter outlines the statistical analyses performed and details the outcomes in chronological order. The chapter concludes with a discussion deliberating the implications of the outcomes reported.

## 5.2 Statistical Analysis

Statistical analyses were performed using SPSS version 20 (SPSS Inc, Chicago, IL), and SAS version 9.4 (SAS Institute; Cary, NC). Numerical values are expressed as mean (SD) for parametric data or median (interquartile range [IQR]) for non-parametric data. Normality of the distribution of data was assessed by visual inspection of histogram and normal probability plot. Non-parametric data were $\log_e$-transformed before comparative analyses. Continuous data were compared using Student t-tests.

Exploratory analyses were performed to identify any potential factors influencing patients' willingness to participate. The information available on invited patients invited was limited to their age, gender, ethnicity, general practice and last recorded eGFR. These five factors were therefore assessed by binary logistic regression using a forced enter method with regard to their impact on patient's research participation. Patients who expressed interest in participating were categorised as 'willing invitees' whereas patients who either did not respond to the invitation or replied but declined participation were grouped together as 'non-willing invitees'. Patients' gender (male/female) and ethnicity (white/others) were analysed as dichotomous data whereas age and last recorded eGFR were analysed as continuous data. Supplementary analyses were performed with eGFR being dichotomised either into CKD stage 3a (eGFR: 45- 59 ml/min/1.73m$^2$) and stage 3b (eGFR: 30- 44 ml/min/1.73m$^2$) or into categories above or below the median of eGFR (54 ml/min/1.73m$^2$). Non-linearity of age and eGFR were examined using restricted cubic spline models. Models were selected on achieving a significant improvement in Akaike's Information Criterion. Statistical significance was defined as a two-tailed p value $< 0.05$.

## 5.3 **Results**

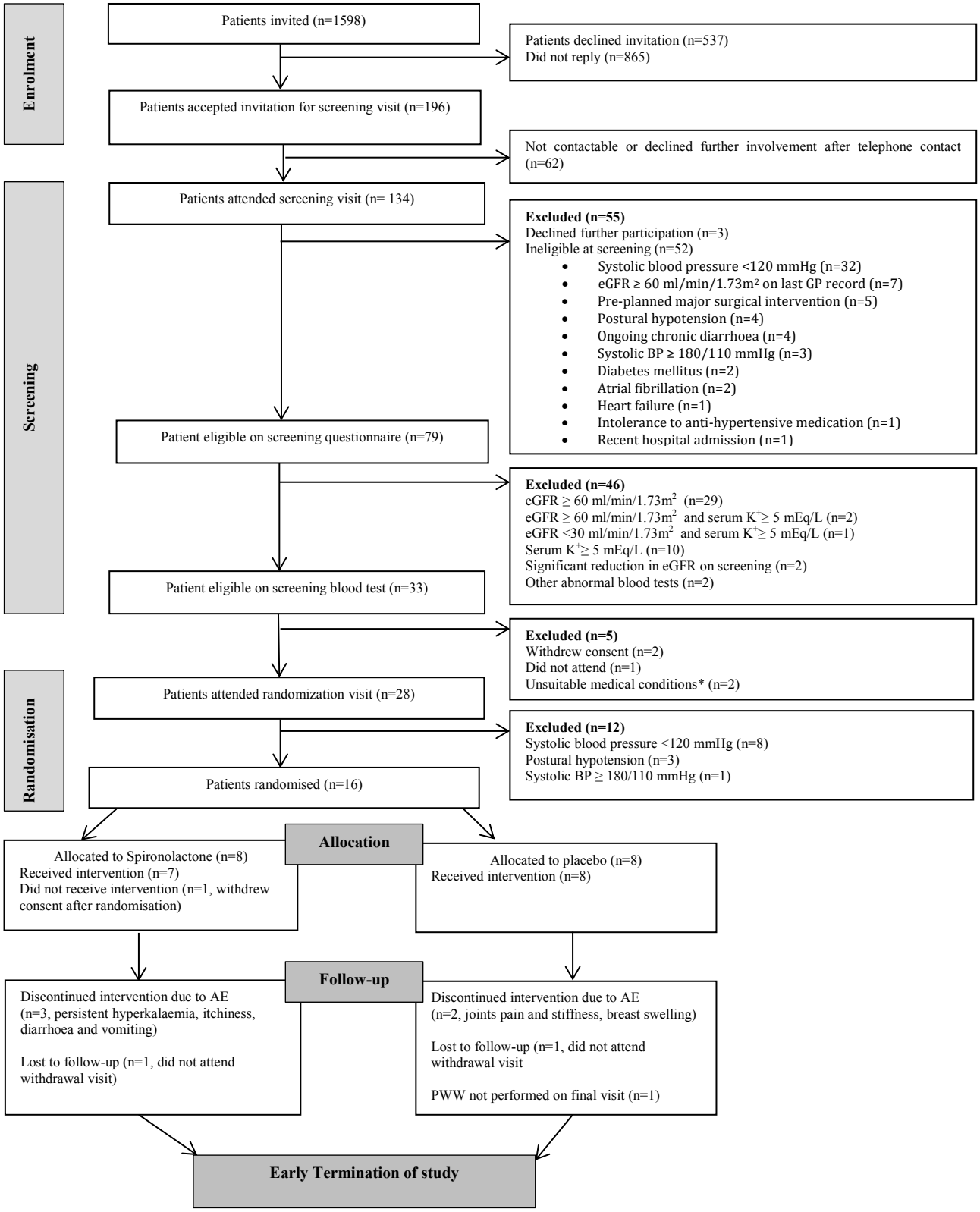
All 71 primary care practices within the former South Birmingham Primary Care Trust with more than 3,000 patients registered were invited to participate. Eleven practices (15%) agreed to take part, with a total population of 112,462 (Table 5-1). Electronic database searches identified 2,044 potentially eligible patients. A further 446 (21.8%) patients were excluded by their GPs with the proportion excluded varying considerably between the practices (2.3 – 52.6%). Five of the 11 practices were known to be 'research-active' and had dedicated research nurses on-site. There was no statistically significant difference in regards to

proportions of patients excluded between ‘research-active’ practices compared to their counterparts (median: 19 [IQR: 10-47] vs 11 [IQR: 4-28] %, p=0.2).

Table 5-1: Eleven recruiting practices' population, prevalence of stage 3-5 CKD, numbers of patients invited, screened and randomised for STOP-CKD study.

| Practice | Practice population | Prevalence of stage 3-5 CKD* | Patients eligible from computerised search (%) | Patients excluded by GP (%)** | Patients invited (%) | Patients replying (%)*** | Patients expressing interest (%)† | Patients attending screening visit (%)† | Patients randomized (%)† |
|---|---|---|---|---|---|---|---|---|---|
| #1[R] | 7,501 | 4.72 % | 260 (3.5) | 49 (18.8) | 211 (2.8) | 105 (49.8) | 37 (17.5) | 22 (10.4) | 3 (1.4) |
| #2[R] | 3,838 | 1.86 % | 38 (1.0) | 20(52.6) | 18 (0.5) | 7 (38.9) | 3 (16.7) | 3 (16.7) | 0 |
| #3 | 27,025 | 4.82 % | 360 (1.3) | 183 (50.8) | 177 (0.6) | 102 (57.6) | 21 (11.9) | 15 (8.5) | 1 (0.6) |
| #4 | 7,113 | 3.58 % | 179 (2.5) | 7 (3.9) | 172 (2.4) | 81 (47.1) | 20 (11.6) | 12 (7.0) | 2 (1.2) |
| #5 | 24,553 | 2.97 % | 478 (1.9) | 97 (20.3) | 381 (1.6) | 152 (39.9) | 41 (10.8) | 29 (7.6) | 5 (1.3) |
| #6[R] | 8,729 | 4.19 % | 157 (1.8) | 17 (10.8) | 140 (1.6) | 61 (43.6) | 20 (14.3) | 16 (11.4) | 3 (2.1) |
| #7[R] | 5,817 | 4.69 % | 129 (2.2) | 13 (10.1) | 116 (2.0) | 44 (37.9) | 15 (12.9) | 10 (8.6) | 1 (0.9) |
| #8 | 4,824 | 3.58 % | 114 (2.4) | 13 (11.4) | 101 (2.1) | 44 (43.6) | 11 (10.9) | 10 (9.9) | 0 |
| #9 | 9,436 | 6.67 % | 236 (2.5) | 25 (10.6) | 211 (2.2) | 97 (46.0) | 19 (9.0) | 12 (5.7) | 0 |
| #10 | 7,104 | 2.75 % | 43 (0.6) | 1 (2.3) | 42 (0.6) | 27 (64.3) | 6 (14.3) | 3 (7.1) | 1 (2.4) |
| #11[R] | 6,522 | 2.97 % | 50 (0.8) | 21 (42.0) | 29 (0.4) | 13 (44.8) | 3 (10.3) | 2 (6.9) | 0 |
| Total | 112,462 | | 2,044 | 446 | 1,598 | 733 | 196 | 134 | 16 |
| Mean % | | 3.89% | 1.82% | 21.8% | 1.42% | | | | |

*[R] Signify general practices which were research-active and had dedicate on-site practice research nurses.*
**Data obtained from Quality and Outcomes Framework 2013/2014 report*
*(%) indicates percentage of total practice population*
*** indicates percentage of potentially eligible patients excluded by their general practitioner*
*†indicates percentage of patients invited*
*Abbreviations: CKD, chronic kidney disease; GP, general practitioner*




* multiple adverse reaction to anti-hypertensive in the past and previous endovascular aortic aneurysm repair which would affect PWV measurements

Figure 5-1: STOP-CKD study consort diagram

### 5.3.1 Invitation to Study Participation

A total of 1,598 invitation letters were sent out to all potentially eligible patients (Figure 5-1). Sixty-three percent were female. The mean age of those invited was 71 (SD: 12) years and median eGFR was 53 (IQR: 48-57) ml/min/1.73m$^2$. Most patients' (84%) last eGFR readings were within the range of 45-59 ml/min/1.73m$^2$. The ethnicity of those receiving invitations was 83.4% white British, 3.4% black British, 3.3% South Asian, 1% mixed or other ethnicity and 8.9% unknown.

### 5.3.2 Patients' Response to Study Invitation Letter

Responses were received from 733 patients (46%) who had a mean age of 73 (SD: 11) years and 34 % were male. Of these, 196 (12%) expressed interest in participating in the study. Percentages of those who were interested in participation ranged from 9% to 18% across the 11 practices (Table 5-1).

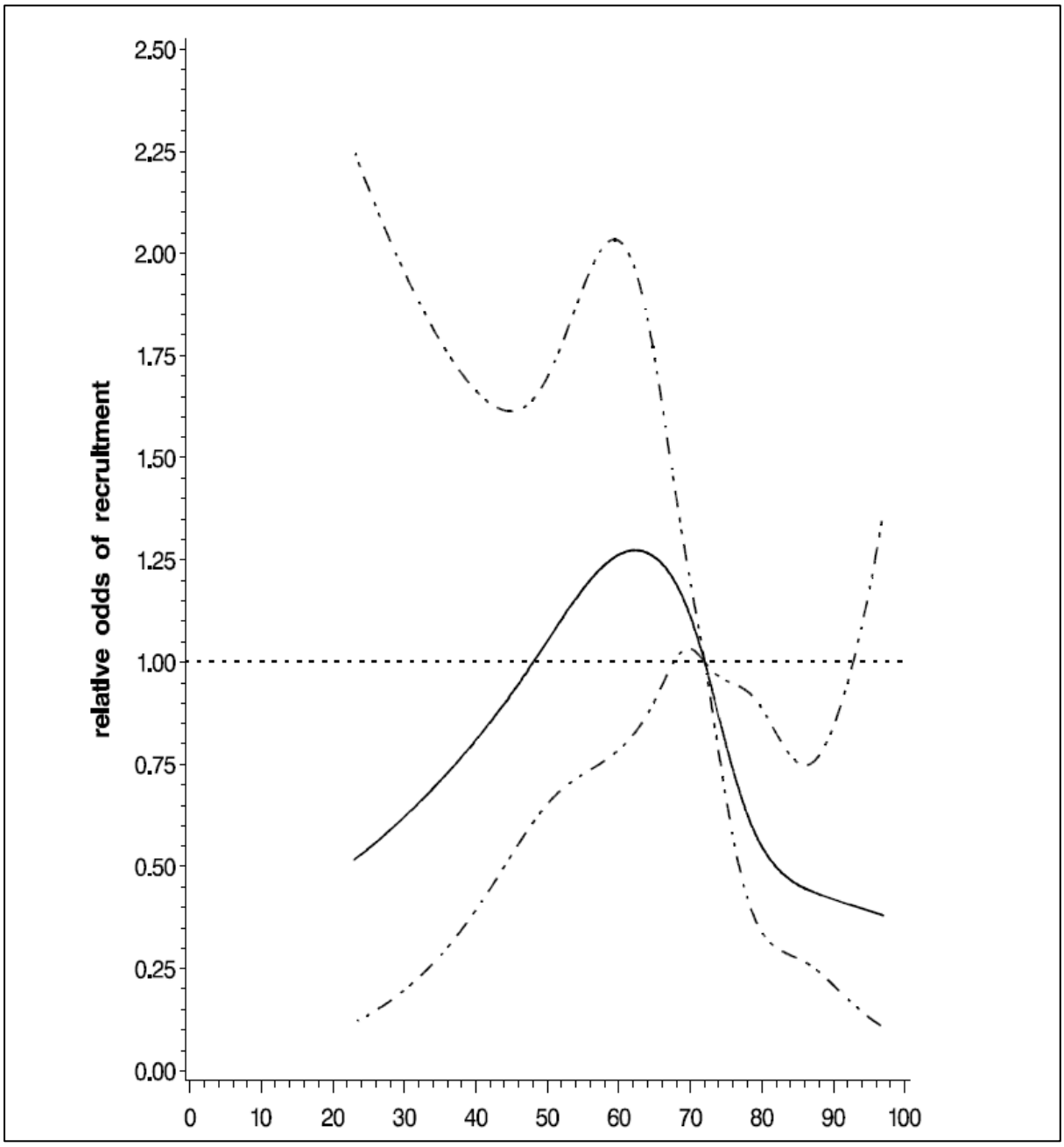
Of the 537 patients who responded declining participation, 295 (55%) did not wish to take a new medication, 220 (41%) did not wish to be part of a research trial, 134 (25%) indicated that they did not have time to take part in the study, 86 (16%) did not wish to have further blood tests, 48 (9%) were unable to attend the surgery, 21 (4%) believed kidney problems were of no concern to them and 80 (15%) did not give a reason. Other reasons for non-participation detailed in the free-text area on the research reply slip included old age, poor mobility, presence of other health issues, concerns regarding the side effects of spironolactone, reluctance to take additional medication, work commitments, being carer for other family members, being away from home during trial period as well as unawareness of CKD diagnosis.

Logistic regression model demonstrated that age, male gender and coming from research-active practices were associated with a greater likelihood to response positively to research invitation, whereas ethnicity and levels of eGFR were not predictive (Table 5-2). Age was noticeably non-linear in relation to recruitment, with younger and older age associated with a lower likelihood (Figure 5-2).

Table 5-2: Logistic regression demonstrating factors associated with increased likelihood of patients' positive response to research invitation. (Age as Restricted Cubic Spline)

| **Variable** | **Odds Ratio** | **Lower 95% CI** | **Upper 95% CI** | **P value** |
|---|---|---|---|---|
| Intercept | 0.01931 | 0.00095 | 0.394 | 0.0103 |
| eGFR | 1.00513 | 0.98076 | 1.030 | 0.6827 |
| **Male gender** | **1.36905** | **1.00544** | **1.864** | **0.0461** |
| White Ethnicity | 1.51474 | 0.96679 | 2.373 | 0.0699 |
| **Research-Active Practice** | **1.42223** | **1.04079** | **1.943** | **0.0270** |
| AGE | 1.02677 | 0.97659 | 1.080 | 0.3014 |
| AGE1 | 0.93568 | 0.79398 | 1.103 | 0.4275 |
| AGE2 | 0.79572 | 0.15232 | 4.157 | 0.7865 |
| AGE3 | 3.30525 | 0.10044 | 108.771 | 0.5024 |
| **P for non-linearity for Age** | | | | **0.0111** |
| **P for overall effect of Age** | | | | **0.0003** |

Figure 5-2: Relative odds and 95% confidence interval of recruitment by age using restricted cubic spline.




NB: Solid line = estimate, dotted lines = 95% CIs.

Nevertheless, a significant proportion (32%) of patients who replied positively to the STOP-CKD research invitation did not, in actual fact, attend the screening visit; they either declined further research involvement after telephone invitation to the screening visit or were not contactable by the research team (Figure 5-1). Hence, further logistic regression was performed to examine factors which were associated with increased likelihood of actual attendance at the STOP-CKD study screening visit (Table 5-3). Compared to the previous model (Table 5-2), age and male gender remained to be strongly associated with actual attendance at screening visit while research-active practice was no longer a statistically significant factor. A trend towards increased likelihood of research screening attendance was noted amongst patients of white ethnicity.

Table 5-3: Logistic regression demonstrating factors associated with increased likelihood of actual attendance at the STOP-CKD study screening visit.

| **Variable** | **Odds Ratio** | **Lower 95% CI** | **Upper 95% CI** | **P** |
|---|---|---|---|---|
| Intercept | 0.098 | | | 0.025 |
| eGFR | 1.008 | 0.979 | 1.037 | 0.599 |
| **Male gender** | **1.521** | **1.063** | **2.178** | **0.022** |
| White Ethnicity | 1.716 | 0.989 | 2.978 | 0.055 |
| Research-Active Practice | 1.352 | 0.937 | 1.951 | 0.107 |
| **P for overall effect of Age** | | | | **0.024** |

### 5.3.3 Screening Visit

Of the 196 patients who initially expressed an interest in participating in the study, 134 patients (69%) actually attended the screening visit. The characteristics of these

patients are presented in Table 3. The cause of CKD was unclear in the majority of the patients and only 17 patients (13%) had a documented cause of CKD. The median last-recorded MDRD eGFR was 55 (IQR: 51-57) ml/min/1.73m$^2$ with 88% within the range of 45-59 ml/min/1.73m$^2$.

In total, 52 (39%) patients were found to be ineligible for the study during the screening visit. The reasons for exclusion are listed in Figure 5-1. The main cause for exclusion was low BP. Thirty-two patients had an office SBP lower than 120 mmHg with 16 patients receiving at least one anti-hypertensive agent, although five of these patients were known to have ischaemic heart disease and thus another potential indication for treatment with these agents other than hypertension. Of the 79 remaining eligible patients, a further 46 were excluded after the screening blood test (Figure 5-1). The main reason for exclusion (31 patients) was having an eGFR greater than 60 ml/min/1.73m$^2$.

### 5.3.4 Randomisation Visit

Of the 33 remaining eligible patients, 28 (85%) attended the randomisation visit (Figure 5-1). A further 12 patients were excluded at this point. Eight had an office SBP less than 120 mmHg, three had postural hypotension and one had uncontrolled hypertension. Sixteen patients were randomised and their baseline characteristics were shown in Table 5-3.

Table 5-4: Baseline demographics, clinical characteristics, blood pressure measurements and biochemistry profiles of patients attended screening visit and patients randomised to receive trial medication.

| | Attended screening visit | Randomised into STOP-CKD study |
|---|---|---|
| **Number of patients** | **134** | **16** |
| Male gender, n. (%) | 62 (46) | 7 (44) |
| White ethnicity, n. (%) | 125 (93) | 16 (100) |
| Mean age (SD), years | 68 (10) | 71 (7) |
| **Medical history,** n. (%) | | |
| • Hypertension | 62 (46) | 5 (31) |
| • Hypercholesterolaemia | 42 (31) | 3 (19) |
| • Coronary heart disease | 17 (13) | 1 (6) |
| • Coronary artery bypass graft/angioplasty | 13 (10) | 0 |
| • Stroke/transient ischaemic attack | 11 (8) | 1 (6) |
| • Peripheral vascular disease | 8 (6) | 0 |
| Total number of comorbidities, median (IQR) | 1 (0-2) | 0 (0-1) |
| **Medications,** n. (%) | | |
| Anti-platelet agents | 34 (25) | 4 (25) |
| Lipid lowering agents | 54 (40) | 4 (25) |
| Use of anti-hypertensive agents | 74 (55) | 9 (56) |
| • Diuretics | 20 (15) | 1 (6) |
| • β-blockers | 20 (15) | 2 (13) |
| • ACEi/ARB | 48 (36) | 5 (31) |
| • Nitrates | 5 (4) | 0 |
| • Calcium channel blockers | 21 (16) | 4 (25) |
| • α channel blockers | 11 (8) | 0 |
| Patients not receiving any anti-hypertensive agents | 60 (45) | 7 (44) |
| **Smoking history,** n (%) | | |
| • Current smoker | 8 (6) | 1 (6) |
| • Ex-smoker | 55 (41) | 7 (44) |
| • Never smoker | 71 (53) | 8 (50) |
| **BP Measurements** | | |
| • Office systolic BP, mean (SD), mmHg | 132 (19) | 133 (10) |
| • Office diastolic BP, mean (SD), mmHg | 79 (10) | 78 (8) |
| • Office systolic BP ≥ 140 or diastolic BP ≥ 90 mmHg, n. (%) | 47 (35) | 10 (62) |
| • Office BP within NICE CKD targets, n. (%) | 54 (40) | 6 (38) |
| • Office systolic BP <120 mmHg, n. (%) | 34 (25) | 0 |
| | | |
| **Number of patients** | **79** | **16** |
| $Na^+$, mmol/L | 141 (3) | 142 (2) |
| $K^+$, mmol/L | 4.5 (0.6) | 4.5 (0.4) |
| Urea, mg/dL | 6.8 (2.0) | 6.9 (1.4) |
| Creatinine, median (IQR), μmol/L | 98 (85-112) | 101 (86-121) |
| MDRD eGFR (median, IQR), ml/min/1.73m$^2$ | 57 (51-65) | 54 (48-57) |
| CKD EPI eGFR (mean, SD), ml/min/1.73m$^2$ | 59 (12) | 53 (7) |
| Urine ACR (median, IQR), mg/mmol | 0.9 (0-2.0) | 0.85 (0.08- 1.95) |
| • < 3 mg/mmol, n. (%) | 62 (79) | 13 (81) |
| • 3-30 mg/mmol, n. (%) | 16 (20) | 3 (19) |
| • > 30 mg/mmol, n. (%) | 1 (1) | 0 |
| $Ca^{+2}$, mmol/L | 2.38 (0.10) | 2.38 (0.13) |
| Albumin, g/L | 46 (2) | 45 (1) |
| Total protein, g/L | 72 (4) | 71 (3) |
| Alkaline phosphatase, U/L | 78 (25) | 79 (17) |
| Alanine Aminotransferase, U/L | 20 (8) | 19 (7) |

*Abbreviations: ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BP, blood pressure,; $Ca^{+2}$,serum calcium; eGFR, estimated glomerular filtration rate; IQR, interquartile range; $K^+$, serum potassium; $Na^+$, serum sodium; n., number of patients; SD, standard deviation.*

### 5.3.5 Early Termination of Study

The STOP-CKD study was terminated early because of unfeasibility. In order to achieve the original planned sample size of 240 patients, the projected number of primary care practices required to be involved in the study would be 145 practices covering a population of more than 1.5 million. After thorough discussion, the trial DMC and TSC collectively agreed that the study was not feasible with the allocated resources. All participants received telephone contacts from the chief investigator informing them of the early closure of the study. They were asked to stop taking their trial medications with immediate effect and to attend study withdrawal visit.

## 5.4 **Discussion**

In the UK, as indeed in many countries, most patients with early-stage CKD are managed in primary care. Many observational studies have established that patients with CKD managed in primary care have several differences compared with patients managed in secondary care (29). They tend to be older with a lower prevalence of proteinuria and more preserved eGFR (29). These differences are important if any intervention shown to be effective for the treatment of CKD in the minority of patients treated in secondary care is rolled out to the community. The STOP-CKD trial was an attempt to establish whether low-dose spironolactone, a treatment shown to be safe and effective in improving surrogate markers of CV risk in patients with CKD managed in secondary care, was equally safe and effective in patients with CKD managed in primary care. Although the study proved not to be feasible, there are several important findings and lessons that can be learnt from it to inform future interventional studies in this population.

### 5.4.1 Estimating the Number of Patients Needed

Assessing the number of patients needed to invite in order to recruit to the sample size is an essential but challenging requirement in planning any study. Recently, a Japanese study explored the use of information technology in predicting the success or failure of study recruitment (30). The study derived the eligible EPR index by dividing the number of eligible patients identified from the EPR by the target sample size. An EPR index of more than 1.7 was reported to have a sensitivity and specificity of approximately 70% and 100%, respectively in predicting recruitment success. However, in spite of a much higher EPR index of 6.7 that should have predicted successful recruitment, the STOP-CKD study failed to reach its target sample size, suggesting that other recruitment issues were involved.

Following the EPR search for the STOP-CKD study, the number of patients deemed suitable for research invitation reduced considerably after GP review. The variation observed in the proportion of patients excluded by the GPs across the practices suggests that there were large elements of subjectivity and inconsistency amongst the GPs in their assessment of characteristics of patients suitable for this interventional study. It is likely that many patients fulfilling the inclusion criteria were excluded at this stage. While the review of the list of potential participants by their corresponding GPs was well-intentioned, significant selection-bias might have occurred during the process and we suggest that in future studies, this step requires revision with clear and transparent criteria.

### 5.4.2 Prevalence of Chronic Kidney Disease

In the UK, primary care physicians are required to keep a register of patients with stages 3-5 CKD as part of the Quality and Outcomes Framework (2, 30). Published data from the participating practices showed the average percentage of total patients on the CKD register was 3.89%, which is lower than the recently published reports from UK research databases of 5.15% (31) and 5.9% (32) using The Health Improvement Network (THIN) and the Clinical Practice Research Datalink (CPRD), respectively and marginally lower than that reported for all English practices over 2010-2012 of 4.3% (33). Nevertheless, it appears that the observed prevalence of CKD is much lower than the 10% figure which was the finding in prospective epidemiological work in the UK (33) and globally (34). It has been suggested that the prevalence of CKD has been significantly overestimated by using a single serum creatinine measurement to define CKD (35) and this has been confirmed in a recent UK study using two creatinine measurements which reported a CKD prevalence of 3.9% (36).

In order to increase patient inclusivity and bypass the issues of un-coded or mis-coded CKD (5), we searched and short-listed all patients with a latest recorded eGFR of 30-59 ml/min/1.73m$^2$ in the preceding 24 months. The serum blood test performed at screening visit served as a confirmation of CKD diagnosis for all eligible patients. Despite having an eGFR within 30-59 ml/min/1.73m$^2$ previously, 40% of such patients were excluded due to an eGFR greater than 60 ml/min/1.73m$^2$ at screening, and therefore, by definition did not have CKD stage 3. Of those who fulfilled the biochemical eligibility criteria, most had only modest reduction in eGFR with a

median eGFR of 54 ml/min/1.73m$^2$ and none were found to have significant levels of albuminuria (37, 399).

Several limitations associated with such computer screening strategy should be highlighted here. In routine practice, blood tests are often performed when patients are unwell. Transient, minor reduction in eGFR to the level of below 60 ml/min/1.73m$^2$, most likely reflecting the temporary change of renal haemodynamic during the period of illness, might therefore occur. Upon recovery, the majority of these patients often return to their baseline eGFRs, especially for those who did not have evidence of CKD. Conceivably, such might be the case for some of the patients who were invited to the STOP-CKD research following the initial computer screening process. Hence, in addition to the well-known fluctuating nature of eGFRs, especially at higher readings (400), as well as the impact of dietary intake of protein on the measurements, it is perhaps unsurprising that out of the 79 patients who were eligible for the screening blood test, 31 were excluded as they do not in fact have evidence of CKD with the repeat eGFR $\geq$ 60 ml/min/1.73m$^2$. Equally, screening for the latest eGFRs might have also missed out patients with CKD stage 3b who might have transient reduction of eGFR to below the levels of 30 ml/min/1.73m$^2$.

Such high numbers of ineligible participants invited to the STOP-CKD study did not only have significant implications on the research resources and finances, more importantly, despite careful wordings in the research invitation letters, it might have also resulted in unnecessary anxiety to the patients. Additionally, as not all patients invited to the study have confirmed diagnosis of CKD, their seeming lack of illness awareness would therefore need to be interpreted with caution during the qualitative

interview study. In retrospect, these issues could potentially be minimised with the use of more than one previous recorded eGFRs. Ideally, on-going effort to improve CKD coding by the general practices will greatly facilitate CKD research in primary care in the future.

### 5.4.3 Blood Pressure

The treatment of hypertension is still the cornerstone of management of CKD, both in terms of CKD progression and the reduction of CV risk (35, 39). In agreement with other studies, we found less than half of patients attending the screening visit achieved both the SBP and DBP target recommended by the NICE CKD guidelines (1). Amongst those with SBP ≥ 140 mmHg or DBP ≥ 90 mmHg, more than 40% were in fact not receiving any anti-hypertensive medication. It has long been believed that lowering office/clinic BP to levels lower than 120/80 mmHg is associated with worse outcomes and increased mortality, especially in the elderly (401). This is reflected in recent guidelines on the management of CKD that recommend BP not be lowered below these levels (36, 37). The results of the recent SPRINT trial challenge these guidelines (402). In the STOP-CKD study, we excluded patients only if they had uncontrolled hypertension (BP ≥ 180/110 mmHg), had evidence of postural hypotension or had SBP of less than 120 mmHg. Although these criteria were in line with current guidelines, in light of the results of the SPRINT trial, future studies might consider the inclusion of such patients.

### 5.4.4 Primary Care Practice Recruitment Strategies

Though we designed the STOP-CKD study to minimize any extra workload on the participating primary care practices, most practices declined the initial approach and it took a lot of effort from one or more of the investigators to recruit the 11 practices

that participated. In order to improve the quality and quantity of primary care research, the NIHR Clinical Research Network and the Royal College of General Practitioners have developed a 'research ready self-accreditation' initiative to support general practices in meeting the legal requirements of the UK for carrying out research (5). Thus far, there are more than 1,000 research-ready general practices in the UK (5). Our study demonstrated a significant positive influence of research-active practices on patients' reply to research invitation providing further support for these measures. Disappointingly, such positive influence of research-active sites did not appear to translate into increased research recruitment. The considerable discrepancy between positive response to research invitation and actual attendance at research screening visit was a noteworthy finding and suggested that other factors were in play during the process. Further research to explore and overcome such issues is clearly warranted.

### 5.4.5 Patient Recruitment Strategies

Although the need for a robust evidence base, usually in the form of RCTs, for any intervention before it becomes accepted practice is now well-established, there is surprisingly little evidence on how best to conduct an RCT (301, 302). Regulatory and ethical issues compelled us to contact potentially eligible patients by mailshot through their GPs. This is a notoriously inefficient and costly process with large number of invitations needing to be sent to recruit the target number of patients. Two key reviews previously explored the value of various strategies in improving participants' recruitment in research studies (6, 41). The STEPS study suggested that being flexible and robust in adapting to unexpected issues was important to ensure trials success (40) whilst in the systematic review by Treweek et al, telephone

reminders to non-responders, opt-out rather than opt-in system of being contacted about the study, financial incentives and open designs all appeared to be effective strategies (40). We suggest that an initial approach using telephone, text or email may yield better results and that further research examining the acceptability and efficacy of initial recruitment strategies is of major importance. Our logistic regression model showed that younger and older patients were significantly less likely to participate. As discussed, the older patients were those we were trying to recruit into the study. This, although we designed the study with broad inclusivity, criteria with the aim of increasing the generalisability of our results, we still did not manage to recruit the "real-life CKD population", which may be reflecting patients' self-selection bias. Strategies to recruit these patients therefore need developing and testing in future studies.

## 5.5 **Conclusions**

The STOP-CKD study was a non-age restricted, investigator-led, feasibility RCT designed to inform a future larger, hard end-point study addressing most of the problems associated with research in CKD populations detailed above. However, such an approach was unsuccessful. The study highlighted the unique characteristics of non-diabetic CKD population recruited in the primary care which challenged our preconceived knowledge about the appropriate intervention and management of this sizeable group of patients. With the majority of interventional studies on CKD populations thus far based in secondary and tertiary centres, there remains an urgent need to optimise the generalisability of future CKD research, especially in primary care. The experience and lessons learnt from this study provide important information for all CKD researchers, especially those in the UK to meticulously reflect on their

future research aims, study design, choices of intervention and most importantly recruitment strategies. As Henry Ford once said, ‘failure is only the opportunity to begin again, only this time more wisely’.

# CHAPTER 6 PATIENTS’ PERCEPTIONS OF EARLY OR MODERATE CHRONIC KIDNEY DISEASE IN PRIMARY CARE

## 6.1 **Introduction**

Though quantitative research is widely known for its strength in generating objective, reliable and generalisable information if designed and conducted with meticulous rigour (403), it is not suitable for investigating certain type of research questions, such as understanding patients' experience or examining barriers to research participation. Characterised by its ability to produce rich, comprehensive and in-depth data, qualitative research is therefore an ideal method to address such complex or unquantifiable social and healthcare research questions (404).

Strauss and Corbin defined qualitative research as 'any type of research that produces findings not arrived at by statistical procedures or other means of quantification' (405). However, the contrast between quantitative and qualitative research is not purely confined to the use of numbers (406). Mohr et al described the distinctive difference with regards to the 'mental model' between the two approaches: quantitative research has a 'variance theory' approach as it deals with 'analysis of the contribution of differences in values of particular variables to differences in other variables', while qualitative research adopts a 'process theory' approach (406, 407). This 'process theory' approach generates knowledge by analysing 'the process by which some events influence others' (406) and convey contextual, explanatory, evaluative and generative data (404). This provides a way of addressing complex issues, which are often difficult or impossible to quantify. In addition, as there is less restriction or assumption placed on the data collected, qualitative studies also allow broader topics to be studied which are not limited to rigidly defined variables and enable in-depth examination of the phenomena using subjective information. Hence, they are useful for hypothesis generating or exploratory research (404).

As both quantitative and qualitative research approaches have their own unique strengths and weaknesses, rather than being in competition, both methods are believed to be complementary to each other (Figure 6-1) (408). Steckler et al proposed four possible ways to integrate qualitative and quantitative methods: 1. Using qualitative methods to help develop quantitative measures and instruments; 2. Using qualitative methods to help explain quantitative findings; 3. Integrating quantitative methods to embellish a primarily qualitative study; 4. Using both qualitative and quantitative methods equally and in parallel (408). When implemented wisely, both methods used in tandem can produce fuller and more comprehensive results. The use of qualitative research is indisputably valuable in closing the knowledge gap not amenable to quantitative research (409, 410).

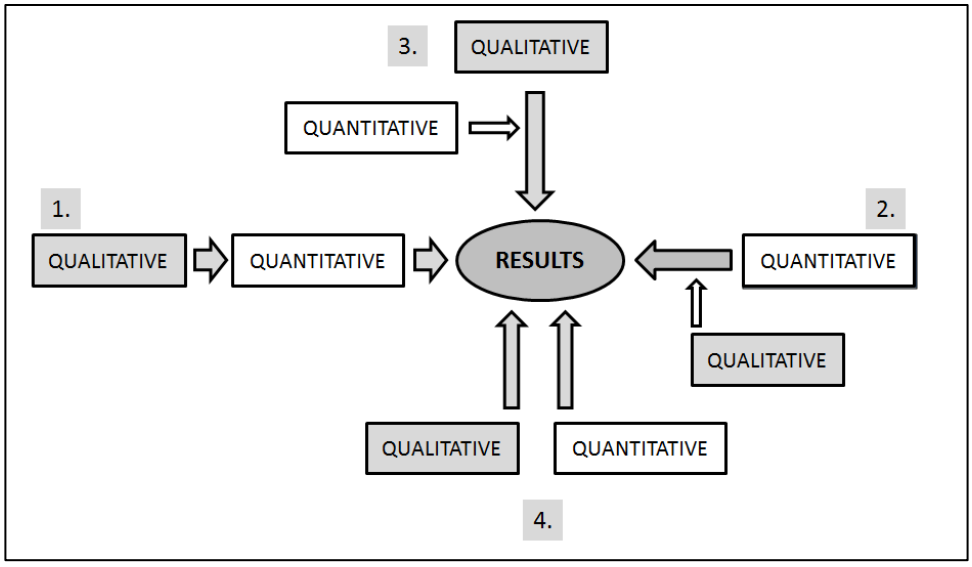



Figure 6-1: Integrating qualitative and quantitative research methods

Although there is an obvious trend of growing awareness and interest in qualitative research among healthcare professionals and researchers (411), a study by Lewin et al

examining the use of qualitative methods alongside RCTs of complex healthcare interventions concluded that the integration of the two methods remained uncommon (412). Disappointingly, even when both approaches were used in combination, methodological shortcomings and poor timing of the qualitative studies were common. Often, findings of the embedded qualitative studies were also inadequately integrated with their corresponding RCTs (412). These reflected under-utilisation of crucial opportunities to better evaluate the effects of the interventions and improve understanding of participants' experience (412).

In this current climate whereby patient-centered care is strongly advocated (413), better understanding of patients' perceptions and experience will undoubtedly be invaluable in guiding healthcare service providers and commissioners to enhance the quality of care provided for patients with CKD. While there has been growing interest and improved understanding of patients' illness perceptions and experience amongst those with ESRD (250, 289), research examining similar issues in patients with early or moderate stage CKD remains very limited. Though disease burden is generally less in patients with early or moderate stage CKD, its significant negative impact on patients' physical and mental QOL is nonetheless noticeable even in its early stages (255).

The qualitative interview study nested within the STOP-CKD pilot RCT therefore aimed to examine patients' attitudes towards CKD and research in CKD in the community setting. Additionally, it also set out to identify potential barriers to research participation and explored potential solutions to overcome the barriers. This chapter describes the qualitative methodology of the interview study and details the

results of the findings on patients' perceptions of CKD. In-depth understanding of patients' perceptions of CKD is crucial and forms the foundation for exploring the barriers to their participation in research studies in the next Chapter.

## 6.2 Patient Recruitment for Interview Study

Patients who were invited to participate in the STOP-CKD RCT were also invited to participate in the qualitative interview study.

A total of 1,598 invitations for the STOP-CKD study were sent out to patients with stage 3 CKD (Figure 6-2). Together with the STOP-CKD RCT invitation letter and patient information sheet, there was a one-page reply slip and a pre-paid envelope for patients to inform the study team of their willingness to participate (Appendix 6-1). Irrespective of their willingness or unwillingness to participate in the RCT study, on the reply slips, all patients were asked if they were interested in taking part in this interview study. The reply slip stated that the interview study aimed to explore people's view about a research study in kidney disease in the community. One hundred patients replied and agreed to be contacted for the interview study. Based on the reply slip, the researcher made contact with willing participants and sent out a patient information sheet regarding the interview study. In total, 17 patients were consented for the study and interviewed.

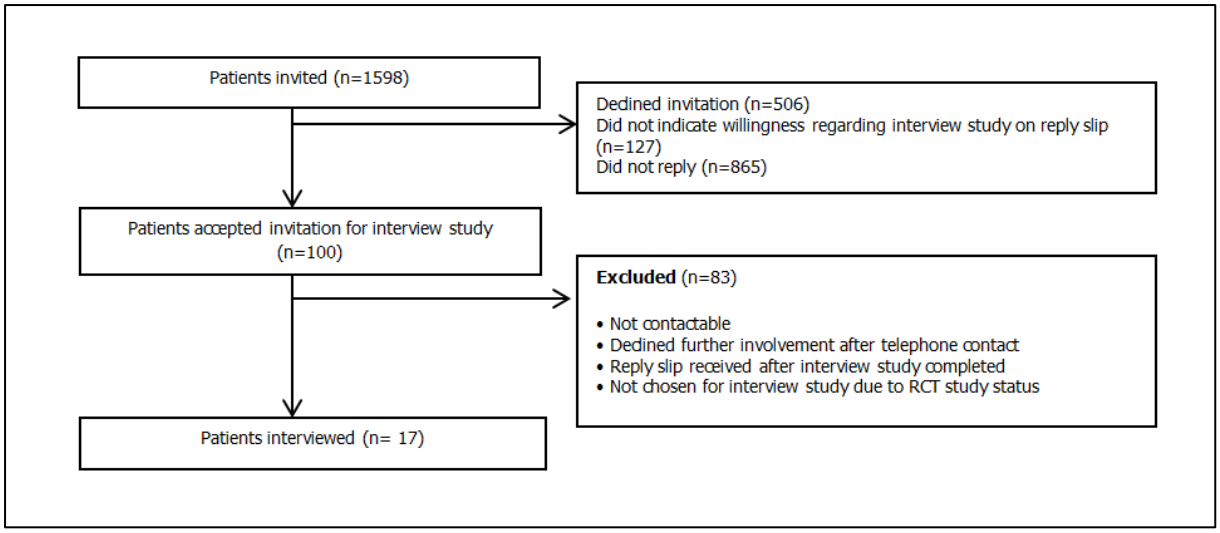



Figure 6-2: Flow chart of patient recruitment for interview study

## 6.3 **Data Collection**

The data was collected using one-to-one interviews. As the qualitative study primarily aimed to examine patients' attitudes towards CKD and research in CKD, in-depth interviews were therefore chosen as the data collection method as opposed to focus groups. Focus groups offer less opportunity for the detailed generation of individual accounts whilst in-depth interviews allow such delicate and complex issues to be explored at a detailed level, enable thorough investigations of each individual's personal perspective and therefore provide an opportunity for in-depth understanding of the personal context within which the research phenomenon is located (404). In addition, understanding motivations and decisions within complex processes are also generally considered to be best addressed in in-depth interviews as it required the detailed personal focus that interviews allow.

The interviews were carried out at a place that was convenient to the interviewees, either at the interviewees' home or in a private consultation room at their primary care practice. Prior to the interviews, the researcher confirmed that participants had correct

understanding of the interview study and obtained informed, written consent from all participants (Appendix 6-2). Interviews involved both patients who agreed or declined to participate in the STOP-CKD RCT. Purposive sampling aimed to include the range of views from participants of different ages, ethnicity and gender (405). These sampling factors were chosen in order to maximise the demographic variation of the data (414). In addition, the research also aimed to achieve phenomenal variation (variation on the target phenomenon under study) in the data by interviewing patients who agreed, declined or were found ineligible to participate in the STOP-CKD RCT (414).

The interviews were semi-structured, guided by a topic prompt (Appendix 6-3); to elicit interviewees' perception of CKD, views on research in primary care and the barriers that exist to research participation. Interviewees were encouraged to openly convey their views. The topic prompt was refined over the course of the study (415) and was pilot tested prior to the interview study. After the first four interviews, it was noted that some interviewees were not aware of their CKD diagnosis. When asked about their understanding of the effect of reduced kidney function, interviewees often highlighted their knowledge gap about their kidney condition. In addition, they also commented on the term 'chronic kidney disease' written on the STOP-CKD RCT research invitation letter. Therefore, several changes were made to the topic prompt in order to incorporate questions to explore patients' awareness of CKD diagnosis, perception of the term 'chronic kidney disease' and perceived knowledge gap about CKD.

All interviews were audio-taped, with the interviewees' permission, and transcribed verbatim. Interviewee transcript review (ITR) is a process whereby interviewees are

provided with their interview transcripts for verification and review (416). As this study aimed to produce data which reflected precisely what was said at the time of the interview, the researcher therefore chose not to perform ITR. In addition, this decision was also made in order to avoid issues with inconsistent data sources or loss of data when the interviewee chose to remove valuable material (416). All transcripts were read and checked for accuracy by the researcher and the text entered into a computerized database using the NVivo (QSR International) qualitative software package for coding and analysis. Interviewing continued until no new relevant knowledge was generated from new participants and adequate data saturation appeared to be achieved (17 interviews) (417).

## 6.4 **Data Analysis Method**

A grounded theory approach was used to inform and guide data collection and analyses (418). Developed by Glaser and Strauss in 1967, grounded theory derives its theoretical underpinnings from Pragmatism and Symbolic Interactionism (405). Pragmatism assumes that 'knowledge is created through action and interaction' whereas symbolic interactionism aims to 'explore behaviours and social roles to understand how people interpret and react to their environment' (405). The grounded theory provides a systematic approach to the analysis of qualitative data and enables the development of theory that is 'grounded' in the reality of the data (418). This grounding of concepts in the data ensures theory-observation compatibility and guards against researcher bias. (419). The key methodological procedures of grounded theory research are an iterative approach, theoretical sampling and constant comparisons during data analysis (Figure 6-2) (405). Corbin and Strauss advocated data collection and analysis as interrelated processes (419). The iterative approach of

grounded theory represents cycles of simultaneous data collection and analysis, in which the results of the ongoing data analysis inform the next cycle of data collection (420). This responsive data collection method based on concepts derived from the previous data collected is therefore termed ‘theoretical sampling’. In contrast to a conventional sampling method which has a predefined sampling population, theoretical sampling is both concept-driven and cumulative (405). Data sources are selected purposively for their potential ability to develop further emerging analytical considerations. (420). With each cycle of sampling bringing in more data to build upon the previous analysis, the subsequent sampling becomes more specific with time until categories reach the point of ‘saturation’. (405). While ‘total saturation’ of data is unlikely to be fully achieved in reality, ‘data saturation’ is generally considered as the point in data collection when new information does not contribute any new insights relevant to the overall model, theory or framework (405).

Constant comparison is the central principle of data analysis in grounded theory research. All issues of interest noted in the data are continuously compared against other examples for similarities and differences (419). This facilitates greater precision and consistency in labelling and grouping of concepts (419). Through this iterative approach and constant comparison process, the grounded theory method allows relevant concepts to be identified as soon as they are perceived and these concepts can then be challenged, expanded, evolved, refined and developed in depth as the study continues (419). With time, such concepts accumulate in number, become more abstract and allow development of categories (419). Described as the ‘cornerstones’ of developing theory, well-defined categories provide explanatory power to facilitate emergence and integration of theory (419).

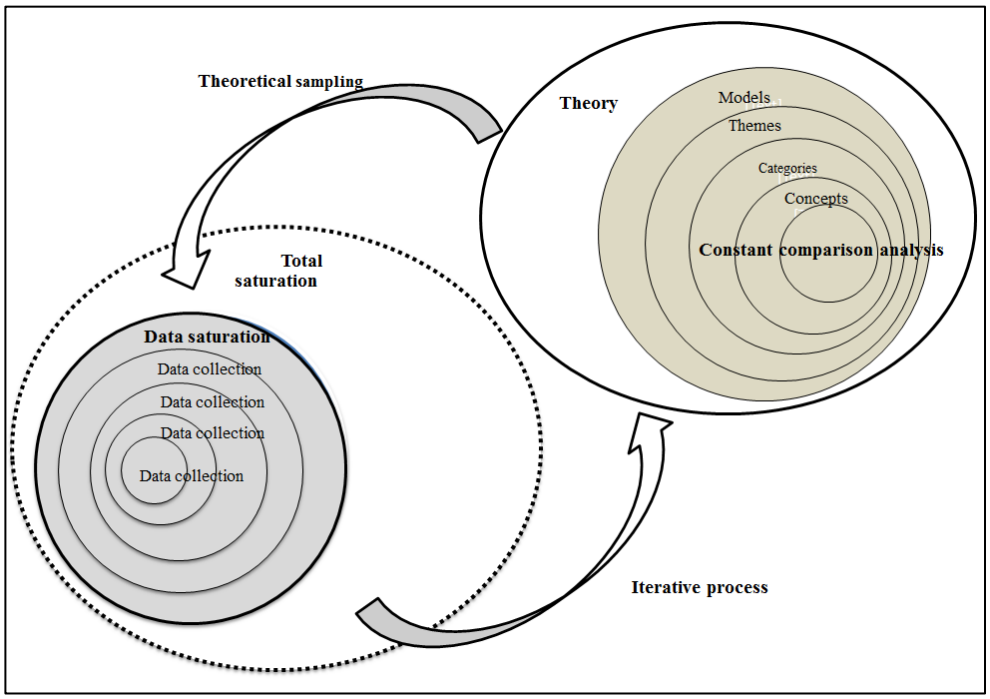



Figure 6-3: Concept of grounded theory approach (405).

Coding forms the basis of data analysis. In qualitative research, a code refers to 'a word or short phrase that symbolically assigns a summative, salient, essence-capturing, and/or evocative attribute' for a portion of data (421). Grounded theory described the use of three basic types of coding: opening coding, axial coding and selective coding (419). In open coding, issues of interest are compared with others for similarities or differences and the conceptual labels (codes) are then assigned to the raw data. As the codes and categories grow, axial coding aims to establish the relationship between the categories and codes. At the later stage of study, selective coding unifies all categories around a 'core' category (419).

The use of numbers in qualitative research has been a matter of ongoing debate. Though several qualitative researchers valued the use of numbers as a complement to an overall process orientation to the research (422-425), concerns about the

appropriateness of its use remain (404, 426, 427). As the sampling strategy in qualitative research does not aim to identify a statistically representative set of respondents, incorporating numbers in results might lead to the inference of greater generality for the conclusions than is justified (406). In addition, it can also detract from the reading style and risk imposing a 'variance theory mental model' on the research which potentially undercuts the strength of the 'process theory' that qualitative research offers (section 6.1) (406). Based on these arguments, this study has therefore chosen mainly to make quantitative claims in verbal form, using terms such as some, several, many, often, typically, sometimes. Numbers were used on limited occasions when researcher felt that its use would complement the reporting of qualitative information.

The findings of this interview study are organised under two main research areas, which are 'patients' perceptions of early or moderate CKD in primary care' and 'factors influencing research participation in patients with early to moderate CKD'. They are presented in chapter 6 and 7, respectively.

## 6.5 **Interviewer Characteristics**

All interviews were conducted by a single researcher (the author). The researcher was a 33 year-old female, of Chinese ethnicity, with good command of English. She was a clinical researcher in CKD and a hospital doctor specialising in renal medicine at a large tertiary referral hospital who was familiar with the diagnosis, treatment and management of patients at different stages of CKD. She introduced herself as a 'kidney doctor who is involved in the STOP-CKD study' to the interviewees and explained that all general queries would be answered at the end of the interviews.

Aware of the potential influence of her professional role as a doctor on the interview (428), the researcher made it clear that she was not involved in interviewees' medical care and did not have access to patients' personal medical information. Therefore, all personal health queries raised by the interviewees were referred to their own GPs.

The researcher was involved in both the recruitment of the quantitative RCT and the qualitative interview component of the STOP-CKD study. Hence, she had prior face-to-face encounter with several of the interviewees who had been screened or recruited in the quantitative RCT before the interviews. Rapport appeared to be achieved more readily with those she had a prior face-to-face encounter with compared to others. However, she attempted to maintain similar structure and coverage during the study with the help of the topic prompts in all the interviews. Being interviewed by a person who was also the 'research doctor' might influence interviewees' level of openness towards the RCT study. The researcher therefore attempted to alleviate the issue by emphasising that one of the aims of the interview study was to try to identify barriers in order to facilitate future studies and therefore encouraging interviewees' opinions and input.

She adopts a subtle realism stance, assuming that there is an objective reality apart from the human knower however, 'our understanding of the world is inevitably a construction from our own perspective or standpoint' (429). Hence, 'one can only know reality from his/her own perspective of it' (404).

## 6.6 **Results**

### 6.6.1 Interview Settings

All interviews with patients were conducted at home, apart from one who chose to be interviewed in a private consultation room at his GP practice. Patients were given the choice regarding the presence of a non-interviewee during the interview. Non-interviewees were present during three of the interviews with the patients (Interviewees #1, #5 and #9) and two of the non-interviewees contributed some of the data generated during the interviews (Interviewees #5 and #9). The duration of the interviews ranged from 12 to 43 minutes.

### 6.6.2 Patients' Characteristics

Of the 1,598 patients invited to participate in the interview study, 100 (6%) patients expressed interest in being interviewed. Of these 100 patients, the majority were of white ethnicity (96 patients), only three patients were Afro-Caribbean and one was Asian. After telephone contact or mailing of interview information sheet to the potential participants, 17 patients responded and eventually agreed to the interviews (Figure 6-1). Purposive sampling of patients with different age and ethnicity were not achieved as the vast majority of patients willing to be interviewed were of older age and white ethnicity. Patients from different general practices and of various levels of involvement in STOP-CKD RCT (see Table 6-1) were therefore purposively sampled for interviews in order to enhance the diversity of the opinions captured in the study.

The majority of the patients interviewed were female and older than 65 years. All interviewees were of white ethnicity. They were from six different general practices in the south Birmingham area. Two patients were enrolled into the RCT; one had

withdrawn from the RCT; one was waiting for a screening appointment; seven were ineligible for the RCT while six declined RCT participation but agreed to the interview study. Interviewees' characteristics are summarised in Table 6-1.

Table 6-1: Interviewees' characteristics

| No. | Age | Gender | Practices | Ethnicity | Participation in STOP-CKD RCT |
|---|---|---|---|---|---|
| #1 | 70 | Male | A | White | Attended screening visit but was ineligible for the study |
| #2 | 65 | Male | A | White | Attended screening visit but was ineligible for the study |
| #3 | 71 | Female | A | White | Attended screening visit but was ineligible for the study |
| #4 | 41 | Female | A | White | Attended screening visit but was ineligible for the study |
| #5 | 71 | Male | B | White | Declined participation |
| #6 | 70 | Female | A | White | Withdrawn from study due to adverse events |
| #7 | 77 | Female | C | White | Attended screening visit but was ineligible for the study |
| #8 | 68 | Male | A | White | In study |
| #9 | 63 | Female | A | White | Attended screening visit but was ineligible for the study |
| #10 | 67 | Male | D | White | Attended screening visit but was ineligible for the study |
| #11 | 80 | Female | D | White | Declined participation |
| #12 | 75 | Female | D | White | Declined participation |
| #13 | 76 | Female | E | White | Await screening visit |
| #14 | 74 | Male | D | White | In study |
| #15 | 69 | Male | E | White | Declined participation |
| #16 | 80 | Female | F | White | Declined participation |
| #17 | 79 | Female | D | White | Declined participation |

### 6.6.3 Interview Themes

Six themes emerged from the interviews with regards to patients' perception of CKD: awareness, explanation provided, emotions, perceived knowledge, views on the term CKD and perceived knowledge gap. Though 'views about the term CKD' came under the umbrella theme of 'knowledge', it was intentionally singled out as a stand-alone emergent theme as it was found to be an influential factor in understanding patients' perception of CKD diagnosis as well as their willingness to participate in the STOP-CKD study. Each theme is summarised in Table 6-2.

All these themes interact with and influence one and another. The relationship between the six themes is illustrated in Figure 6-3. Patients' perception of CKD encompasses awareness, emotions and their perceived knowledge of the diagnosis. All of which in particular, the awareness of diagnosis, are influenced by the explanation (or the lack of explanation) received. Conversely, patients' existing knowledge regarding the effect and long-term implications of reduced kidney function as well as their views on the term 'CKD' were also found to affect their diagnosis awareness and emotions. As patients with early or moderate stage CKD are often asymptomatic, for those who perceived CKD as a severe, debilitating illness, some rejected the diagnosis due to the incongruence between their perceived knowledge of CKD and their current state of health. Whilst for others who accepted the diagnosis, such perceived knowledge of CKD invariably resulted in significant negative emotions.

During most of the interviews, patients expressed their illness experience or views on CKD in the sequence of illness awareness, explanation provided and emotions reactions towards the diagnosis. These were then followed by the researcher further exploring their views on the term 'CKD' and their perceived knowledge as well as perceived knowledge gap. Hence, the flow of the themes are presented in the manner which represents both the order of how the story was unveiled and the gradual increasing depth of data providing understanding of patients' perceptions of CKD.

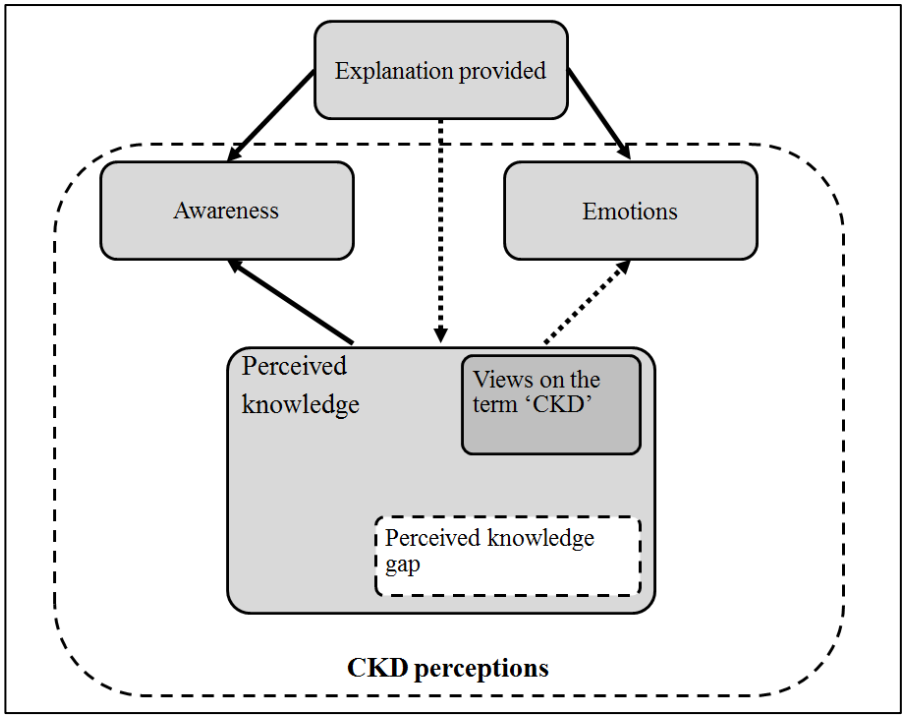



Figure 6-4: The relationship between themes of patients' perception of chronic kidney disease.

Table 6-2: Descriptions of the emergent themes on patients' perception of chronic kidney disease.

| Theme | Description |
|---|---|
| **Awareness**<br>• Related to long-standing renal condition<br>• Related to other illness<br>• Incidental finding during routine blood test<br>• From STOP-CKD invitation<br>• Unaware | Patients' awareness of their current kidney function, their diagnosis of CKD and how they were made aware of their kidney condition. |
| **Explanation provided**<br>• By hospital doctors<br>• By GP<br>• By Research team | The information and explanation provided by the healthcare professionals to the patients' regarding their CKD diagnosis. |
| **Emotions**<br>• Unaffected<br>• Fear<br>• Concerned | Patients' emotional reactions when they became aware of their diagnosis of reduced kidney function/CKD. |
| **Views on the term 'chronic kidney disease'**<br>• Patients' definition of chronic kidney disease<br>• Emotional reaction to the term<br>• Suggestion of alternative terms | Patients' view of the term, chronic kidney disease and their emotional reaction towards to the terminology. Patients were also asked to suggest a more appropriate alternative to describe the condition if they disagreed with the use of the term. |
| **Perceived knowledge**<br>• CKD and ageing<br>• Symptoms of reduced kidney function<br>• Need for dialysis<br>• Need for transplant<br>• Impact of quality of life<br>• Impact of life expectancy | Patients' existing knowledge regarding the effect of reduced kidney function and its long-term implications. |
| **Perceived knowledge gap**<br>• Current level of kidney function<br>• 'Dangerous level' of kidney function<br>• Cause of CKD<br>• Implication of CKD diagnosis<br>• Lifestyle and diet advice | Patients' perceived knowledge gap of their current kidney condition or overall knowledge of kidney disease. |

#### *6.6.3.1 Awareness*

CKD, in its early and moderate stage, is usually a silent condition. The diagnosis is often made as a result of an incidental finding during routine blood tests or while investigating for other illnesses. The majority of patients with CKD remain asymptomatic, unless the disease progresses to the advanced stage (ESRD) which occurs only in a minority. Hence, understanding patients' awareness of the diagnosis of their kidney condition is the crucial first step in gaining deeper insight into their perception of CKD.

However, not all CKD diagnoses were accidental findings. Several interviewees had an established cause of kidney disease, for instance, unilateral nephrectomy due to a kidney tumour (interviewee #8, #14) or kidney stones (interviewee #4, #15). Invariably, these patients have been through extensive investigations in the secondary care setting and were followed-up closely after the operation was performed.

> *"So I had one kidney taken away and everything else and then I was under the consultant there for about two years or more looking at, seeing how I progressed and everything else and various blood tests." Interviewee #14*

Though these interviewees were aware of their 'kidney condition' and were able to explain in detail the events leading up to the diagnosis, it was intriguing to find out that three of these four interviewees (interviewees #8, #14 and #15) did not perceive themselves as having CKD.

*"I don't know really because I haven't got chronic kidney disease as far as I know. I had kidney stones years and years ago and it caused a blockage and therefore one of my kidneys stopped working. So that's what my problem is. That is all I know really." Interviewee #15*

*"I don't think of myself as having (chronic kidney disease), no, I don't think so, no. I think I have moderate probably kidney disease." Interviewee #8*

Some of the interviewees were informed by their GP of their reduced kidney function as part of routine blood tests. More often than not, the wording of 'kidney function being slightly reduced' was being used by the GP when informing patients rather than the term CKD.

*"Well, the last 3 to 4 years, when I've had my MOT, as you call it, which we refer to it, my doctor has said to me that there's a slight failing of the kidney..." Interviewee #1*

Nonetheless, not all patients were aware of their diagnosis of CKD. Several patients were only made aware of their CKD diagnosis when they received the invitation for the STOP-CKD study.

*"Well, I went to the doctors and I had a blood test. I never heard any results of it. The next thing is what I had off you, the letter off you saying your kidney function is low…" Interviewee #5*

In addition to the varying levels of awareness of kidney diagnosis among the interviewees, it was also noted that there was clear discrepancy between awareness of 'kidney problems' and awareness of the CKD diagnosis among the interviewees. The term CKD was often not brought up by the GP to the patients when explaining the findings of their reduced GFR on the blood tests. Upon receiving the STOP-CKD invitation letter, while some patients were alarmed by their unexpected diagnosis of CKD, others remained adamant that the term CKD was not applicable to them as they felt 'too well' to be labelled with such a term. Consequently, some of the patients regarded the STOP-CKD study as irrelevant to them, even those who knew there was 'slight failing of their kidney functions', and therefore chose not to participate in the RCT. Such rejection of the diagnostic label of 'CKD' is a noteworthy and crucial finding among this group of patients and appeared to be influenced by their 'views about the term CKD'. This is further explored in section 6.4.6.

#### *6.6.3.2 Explanation Provided*

Though not all interviewees in this study said that they were informed of their diagnosis, among those who were, the researcher explored the explanation they recounted being given when they were informed of their reduced kidney function or diagnosis of CKD.

When the automated reporting of eGFR was first implemented, some GPs were not fully convinced of the usefulness of the test. One of the interviewees clearly described the frustration and uncertainty he sensed from his GP when the blood test was initially offered to him a few years ago. Nonetheless, he was unsure of the exact reasons underlying such uncertainty.

*"He said there is this test you can now have for kidneys. He said but sometimes it can be a little bit of a nuisance sort of thing, so why I don't know." Interviewee #11*

One of the patients was given an explanation about the fluctuating nature of the eGFR test and was reassured about the finding of a reduced eGFR. The same patient was also told that it might be related to the medication he was taking.

*"(He) said my kidney function was a lower figure than what it was previously, but as long as it keeps filtering and it keeps me alive I don't mind too much, but they did explain that it can fluctuate – next year it could be different – it could be up again… … Again, of course, you ….. it depends upon what medication you are on, I mean there is no medication you take without having some adverse effects, and I'm on Lisinopril, which is for blood pressure and that, I believe, can have certain adverse effects, although slight, on kidney function." Interviewee #2*

In general, one of the most common explanations received by the interviewees was that CKD was part of the ageing process.

*"They just said your kidneys look slightly down on what they used to be, but that comes with age." Interviewee #1*

While some interviewees accepted the brief explanation that reduced kidney function was just an invariable effect of ageing, one interviewee clearly felt that further information and elaboration was warranted.

*"Yes, well I think the letter that was sent out highlighted that kidney function goes down in connection with age but then I think to myself, well there is (are) an awful lot of the various functions that we have that go down with age but I think perhaps that might be useful if there were more information available..." Interviewee #17*

Nevertheless, some of the interviewees did not recall a detailed explanation of their blood test results (eGFR) by their GP but they were often reassured that it was not of any significance.

*"I was told that my blood sample wasn't quite right, but nothing significant, nothing to be concerned about." Interviewee #3*

Patients with early or moderate stage CKD, especially in the elderly population, are known to have far greater risk of CV disease and death than progression to ESRD. Although some patients were made aware of the importance of regular surveillance in order to monitor for any decline in the kidney function, the majority of the patients were not informed of the long-term implications of CKD on the CV system.

*"Not really. He didn't seem to think, provided it did not deteriorate anymore, because I think, I don't know, I forget what the level is now, I can go down to 10% before it is critical really so there is still a way to go before I would be in any trouble ..." Interviewee #8*

Overall, interviewees recalled different aspects of information given regarding their diagnosis of reduced kidney function. The overriding features of the theme are the lack of awareness of CKD diagnosis and the perceived reassurance from their GPs regarding the condition. While a brief, reassuring explanation might be adequate for some patients, others clearly could have benefited from further explanation, elaboration and discussion. In addition, an over-focus on reassuring the patients might also distract both the GPs and patients from discussion of other key issues related to the CKD diagnosis.

#### *6.6.3.3 Emotions*

Interviewees' emotional reactions towards their CKD diagnosis were heavily influenced by the explanation provided as well as their views on the term CKD. The emotions interviewees experienced were of two kinds: alarm or acceptance. While some patients described only one emotion, others recounted their emotional transition from alarmed, worried and concerned to acceptance. Reassurance from the GPs was often associated with a more positive emotional response (i.e. acceptance) from the interviewees. However, the frequent omission of the term 'chronic kidney disease' by the GPs during their explanation of diagnosis occasionally caused a delayed outpouring of anxiety among some of the interviewees as they considered 'slightly low/reduced kidney function' and 'chronic kidney disease' to be of two complete different entities.

When interviewees were told that their reduced kidney functions were related to ageing, many accepted the explanation and were not overly concerned. The absence

of symptoms to ascribe the diagnosis to appeared to have also decreased the significance of the condition perceived by the interviewees and lessened their anxiety.

*"Well, the fact that I was…. well you know, I mean I know we all grow old and things start to fail me, so I thought well if it comes with age then you've just got to take it." Interviewee #1*

*"Just accepted it, I wasn't having any problems so why worry about something that might not happen." Interviewee #3*

Nevertheless, as explanations given to the patients often appeared to be brief, patients' perceived knowledge gap could potentially lead to uncertainty and anxiety. Despite an initial feeling of indifference about his diagnosis, one interviewee started to question his own emotions on further probing.

*"Not unduly worried. Erm… no I wouldn't say so. I mean, when should I be unduly worried? I mean, how would you know if you should be unduly worried? What are the signs and symptoms that you may come across? Is it excessive tiredness, excessive drinking, dryness?" Interviewee #2*

In contrast, some interviewees described fear and anxiety when they first found out about their diagnosis of CKD. One of the interviewees who used to work as a health-care assistant in a haemodialysis unit likened the diagnosis to a death sentence. She portrayed vividly the upsetting complications and the inevitably shortened lifespan patients receiving haemodialysis suffered. Such experience undoubtedly evoked a strong negative emotion when she was made aware of her condition.

"*First thing is 'God, am I gonna die?'... And then you think to yourself, you feel like have I got a death sentence? It must be the same kind of feeling as when you know you've got cancer. I mean I know it's not as bad, but you know, you think to yourself – am I gonna die? That's your first thought." Interviewee #4*

However, after she was reassured by her urologist and nephrologist that she was unlikely to require haemodialysis in the future, her fear and concerns dissipated.

*"I'm quite positive now, I'm ... but you know when you first think, oh god – I've got a death sentence." Interviewee #4*

As some of the interviewees were unaware of their diagnosis of CKD, they were shocked by the invitation letter for the STOP-CKD study. The unexpected diagnosis conveyed in the form of a research invitation letter was frightening for these interviewees. Without prior notification from the GP regarding their kidney function and the absence of any kidney-related symptoms, the interviewees undoubtedly found it hard to accept the diagnosis.

*"Well it is a little bit of concern when you get a letter. I've just had a…. not long had a blood test and then you get this letter saying, you know, noticed in your blood when you had your last blood test at the doctors, there's chronic disease. I thought whoops, you know, they've sent this out to the wrong person." Interviewee #6*

*"I was surprised when I had the letter. My doctor had never told me I had got problems at all and I don't feel I have problems so it came as a bit of shock." Interviewee #13*

Even among those who had been informed by their GP of their recent kidney function test and were unperturbed by the diagnosis previously, one interviewee was still alarmed when he received the STOP-CKD invitation as he assumed that his kidney condition had significantly deteriorated for him to be labelled with CKD.

*"I was very blasé when he (patient's GP) told me. I wasn't frightened of anything. I don't know whether I should have been. The only thing was I suppose I was a little bit, I wouldn't say shocked that is a bit strong, but I was a bit alarmed and I had something from yourselves (STOP-CKD invitation letter) that said critical, critical (chronic) kidney…He (patient's GP) didn't use that word chronic…" Interviewee #10*

As expected, interviewees' emotional response was closely linked to how they were made aware of their CKD diagnosis and the explanation given. A few of the interviewees found out about their CKD diagnosis as a consequence of kidney tumours or kidney stones disease. These patients were seen and cared for mainly by the secondary care centre and they invariably went through the initial emotional phase of shock (due to diagnosis of kidney tumour) to a later phase of acceptance. In contrast, interviewees who were informed of their reduced kidney function as an incidental finding and were reassured by their GPs were relatively unaffected by the diagnosis. Some accepted it as an inexorable by-product of ageing and therefore felt that there was no reason to be worried since they 'couldn't do anything about it'. In

addition, the lack of any perceived kidney-related symptoms also seemed to have reassured the interviewees. However, those who had only realised their CKD diagnosis via the STOP-CKD research invitation letter were understandably shocked and upset on realisation of their diagnosis. Interviewees typically equated CKD to a form of severe, advanced illness. Denial of the diagnosis was evident among a few interviewees as they 'felt too well' to have CKD while some interviewees described resentment towards their GPs as they were not informed of any kidney problem prior to the research invitation letter.

#### *6.6.3.4 Views on the term 'Chronic Kidney Disease'*

An interesting observation which arose during the study was that not only were a significant proportion of the interviewees not aware of their diagnosis of CKD, but among those who were informed by secondary or primary healthcare providers of their kidney condition, the majority did not believe that the term was applicable to them. Most of the interviewees only encountered the term via the STOP-CKD invitation letter. Thus, the interviews explored patients' views on the term 'chronic kidney disease' in order to examine the issues underpinning the above finding.

The majority found the term 'chronic kidney disease' alarming and frightening. In medical terminology, chronic is an adjective relating to time and is used to define any illness that is persistent or constantly recurring (430). Knowing chronic meant permanent and incurable had triggered fear in one of the interviewees.

*"It is a shock to actually know, you know, that you've got something that you've got to live with for the rest of your life." Interviewee #4*

Though a few patients had correctly understood the meaning of 'chronic', a number of patients assumed that it defined the severity of an illness and believed that it denoted 'critical', 'bad' or 'very severe'.

*"Chronic? Erm… it's bad and they just keep failing… you know kidney disease yeah, but chronic kidney disease, it's a bit alarming really." Interviewee #6*

*"Chronic to me is a level that is much higher than kidney disease. It is a level that has gone beyond the point of just having a little bit of kidney disease. Being in chronic; you are right at the top end of the kidney disease." Interviewee #10*

As many of the interviewees perceived CKD as a severe, advanced form of kidney disease, they believed that any patients with CKD would indisputably be suffering from all the ill-effects of having minimal or no kidney function. This perceived state of extreme ill-health related to CKD diagnosis was so distant from interviewees' current state of health that they instinctively dissociated themselves from the label of CKD. One interviewee even felt the need to offer sympathy to 'those with CKD'.

*"Chronic kidney disease, chronic kidney disease, I would think really is the worst type. The people who really need the new kidneys or something, whereas with me I feel, no, I don't need that…" Interviewee #13*

*"Well I am sorry for anybody who has it". Interviewee #12#*

Besides having strong negative reactions to the word 'chronic', some interviewees also expressed trepidation about 'kidney disease'. Kidney disease was equated to kidney failure among some of the interviewees and some also believed that it signified imminent death.

*"I think chronic kidney disease would probably be chronic kidney failure sort of thing." Interviewee #14*

*"Kidney disease means you are going to die if you don't deal with it." Interviewee #12*

In addition, one interviewee also associated the word 'disease' with something contagious.

*"I think straight away the first thought in your head is you know you say you've got a disease, you think, am I contagious?" Interviewee #4*

After the researcher collected interviewees' views on the term CKD, she went on to explain the true meaning and the medical definition of the term. They were then asked if they considered the term CKD as appropriate or whether an alternative term should be used instead to describe the condition, especially in the early/moderate stage. While one interviewee believed that the term CKD was an appropriate medical term provided it could be explained to the public clearly, others suggested changing the

word ‘chronic’ or the word ‘disease’ to alternative terms, for instance, ‘slight kidney disease’, ‘mild kidney disease’, ‘manageable kidney disease’ or simply ‘kidney disorder’.

> *“Well, I would call it manageable kidney disease because it is managing on medication on that basis. Manageable that is how I would describe it now on that basis. It is almost like a set of traffic lights your red, green and amber type thing. Green you are okay fine, amber half and half type thing and red and you are chronic on that basis type thing.” Interviewee #14*

Strong negative perceptions of the term CKD were closely linked to interviewees’ emotional reaction when they received the STOP-CKD research invitation letter, even among those who were aware of their reduced kidney function previously. Emphasis was laid upon the word ‘chronic’ which the interviewees perceived to have a strongly negative connotation. Though in medical terminology, chronic purely denotes long-standing, (in contrast to acute), according to the Oxford Dictionary, ‘chronic’ has also been used informally to describe anything of poor quality (431). This perhaps helped to explain interviewees’ refusal of the CKD diagnosis and hence non-participation in the STOP-CKD study.

#### *6.6.3.5 Perceived knowledge*

Patients’ knowledge of the location and the functions of the kidneys as well as their understanding of the effects of reduced kidney function were explored in this study. The majority of the interviewees had vague ideas of the location of the kidneys and believed that they are around the middle of the back or sides of the abdomen. Most

also understood the basic, key functions of the kidneys. Interviewees described kidneys as the 'filter for the body', associated with the 'water-works' of the body which work to remove the waste products.

*"Well, I understand that they obviously purify your blood and that lots of things pass through your kidneys to clear them of toxins and things like that, yes." Interviewee #16*

In addition, interviewees were also asked about their knowledge of the effects of reduced kidney function and its long-term complications. As most of the interviewees were aware of the main function of the kidney, they commented that the reduction of kidney functions would result in reduction of urine output, deterioration of health and inevitably lead to the 'build-up of toxins in the body'. Some interviewees also went on to point out the consequent need for dialysis treatment, kidney transplant or even death.

*"You're going to get a build-up of toxins in your body, which means you're going to go into kidney failure and then might have to have removed or get an artificial kidney." Interviewee #3*

*"Well, very ill health. Big problems! I mean, can be death obviously." Interviewee #18*

Some also commented on other issues associated with reduced kidney function, for instance, 'blood in the urine', hypertension, lethargy and reduction of quality of life. In general, most perceived it as a serious, life-threatening condition.

*"Well, I think high blood pressure and general reduction in energy and everything that goes with you know being alive." Interviewee #17*

*"Well I haven't come across it a lot but I understand it is in its worst aspects, quite serious and it can alter you know your condition and quality of life." Interviewee #16*

Interestingly, one interviewee was aware of the impact of CKD on arteries based on the experience of his relative with kidney disease.

*"I think it reduces flow of blood to the extremities of your body, like your toes, your hands and things like that where…. I am only saying this out of experience of an aunt of mine who is a diabetic which it's the same sort of thing, it has an effect on the kidney and unfortunately for her, her arteries narrowed, or whatever it does do and she has had an amputation…Now that is what I call chronic." Interviewee #10*

Though several of the interviewees sounded uncertain when they were asked about the effects of reduced kidney function, the majority of them did have good understanding of the impacts of advanced CKD. The description 'reduced kidney function' was often used loosely throughout the interviews by the researcher to denote any severity of CKD, however, as mentioned under the themes 'awareness' and 'explanation provided', interviewees appeared to perceive the two descriptions,

'slightly low/reduced kidney function' and 'CKD', rather differently with the former seemingly being a much less severe, less significant condition compared to the latter. Nevertheless, when they were asked about the effects of 'reduced kidney function', the majority of the interviewees described a rather advanced condition and portrayed a bleak outlook, which they would not apply to themselves. The significant disparity between patients' perception of their own 'slightly reduced kidney function' diagnosis being a much less severe medical condition than their general view of 'reduced kidney function' among some of the interviewees was clearly a noteworthy observation.

#### *6.6.3.6 Perceived Knowledge Gap*

In the midst of the interviews, some interviewees began to ask the researcher various questions in relation to their kidney function, CKD diagnosis and its implication. These included those who had apparently received diagnosis information, explanation and reassurance from their GPs previously. As GPs' consultation time was limited, some felt that they 'did not want to waste their GPs' time by asking more questions.

Understanding CKD to be a long-standing illness, information regarding lifestyle- or diet-change to improve or prevent any decline in their kidney function were topics that emerged repeatedly during the study. In addition, one interviewee also commented on the conflicting information he encountered regarding dietary restriction and said he would appreciate clarification from the healthcare professionals.

*"Yes, I probably should have asked if there was anything I can do, as I did with my angina - I knew I'd got to pack up salt or as the hospital said, salt - cut down, cigarettes, alcohol, exercise, you know." Interviewee #1*

Another commonly raised question was regarding the cause of their CKD, especially for one interviewee whose father died of kidney cancer.

*"If I have got reduced kidney function, then why have I got it? I got a bit scared about it really because I lost my father to kidney cancer…" Interviewee #9*

Prognosis, progression, frequency of monitoring and long-term implications of having CKD were other areas where the interviewees felt they had been poorly informed.

*"If my kidneys aren't as good as they were what can I expect to happen?" Interviewee #1*

*"Whether it is detrimental to my health, if not now perhaps but a little later on and if you can sort of find that out, yes I would prefer to know." Interviewee #13*

*"How do you know if the kidney…. If the number fluctuates, and there's a year intermittently, how do you know that there's no damage going on between the next examination and the previous one? Is a year safe?" Interviewee #2*

While one of the interviewees simply wished that her GP had told her about her kidney diagnosis, others were keen to find out more about their current level of

kidney function as well as the different stages of CKD. As CKD encompasses a wide spectrum of severity, interviewees clearly felt it was important to be informed about the scale of their own condition.

*"I don't really know the extent of my kidney function and what it means to me. I don't know what my level of…" Interviewee #10*

*"Nobody's ever told me what stage I'm on, because obviously we have patients and like they'll have like CKD stage 3 or something, and like I don't understand the stages…" Interview #4*

Nonetheless, a simple description of kidney function in either numerical (i.e.: 52, 47, etc.) or ordinal scale forms (i.e.: mild, slight, etc.) did not appear to be adequate for some of the patients. Without knowing the breadth of the disease spectrum and how far or close they were to the all-important 'critical level', some interviewees struggled to relate to this information in isolation.

*"Numbers mean nothing to me unless you explain what it means, then, like, 47 could be dangerous…. don't know, what is the danger level?" Interviewee #2*

*"He said it is just a little bit low but nothing you know. How low is low, I don't really know." Interviewee #5*

Though one interviewee did not know exactly what his current kidney function was, he recalled being told and reassured that he was far from reaching the 'critical stage'.

*"I forget what the level is now, I can go down to 10% before it is critical really so there is still a way to go before I would be in any trouble." Interviewee #8*

When asked if having a kidney condition affected interviewees' life, some found it a surprisingly difficult question to answer as they were unsure of the signs and symptoms related to CKD. They wondered if some of the common symptoms they experienced in day-to-day life, for instance, lethargy, back pain, joint pain or change of urine colour, could be attributed to their kidney condition. In addition, some were also concerned if there were any red-flag signs and symptoms associated with worsening kidney function which they should be aware of.

*"I get a bit of backache occasionally, is that related to kidneys?" Interviewee #5*

*"I mean, when should I be unduly worried? I mean, how would you know if you should be unduly worried? What are the signs and symptoms that you may come across? Is it excessive tiredness, excessive drinking, dryness?" Interviewee #2*

While the majority of the interviewees mainly focused on their self-perceived gap in knowledge, one interviewee brought up the issue of public education on kidney disease.

The perceived knowledge gaps among all the interviewees covered a diverse area. Interestingly, there was no consistent association between explanation provided and perceived knowledge gaps. Two of the interviewees did not feel that they required

further information regarding their kidney condition: one had been informed about the importance of blood pressure control and monitoring and was reassured about his level of kidney function while the other interviewee only recalled being told that her kidney condition was of no significant concern. These two patients clearly recounted two very distinct explanations provided when they were made aware of their kidney diagnosis but both were satisfied with their current state of knowledge for two very different reasons: one was fully-informed while the other did not feel the need of further information as she was asymptomatic. This demonstrated the complex interaction between the awareness and the perception of self-knowledge.

This once again emphasised the well-known fact that the breadth and depth of the information required by patients are very heterogeneous. What one deemed to be adequate reassurance and information (i.e. slightly lowered kidney function), others might yearn for further clarification if given the chance. In addition, providing information which is context-sensitive and easy to relate to is also crucial in facilitating patients' retention of the information provided and minimising uncertainty or anxiety amongst the patients.

## 6.7 **Discussion**

Illness perception among the early to moderate stage CKD population has been an under-researched subject. This interview study elicited six main themes in regards to patients' perception of CKD: *awareness, explanation provided, emotions, knowledge, views on the term CKD and perceived knowledge gap*.

Though CKD is prevalent in the ageing population, the general public often do not consider the condition as one of the top health concerns (432). Even amongst patients with CKD, awareness has been shown to be suboptimal and it was reported to be as low as 10 -15 % in some studies (433-436). It is therefore crucial to explore the possible factors underpinning this issue.

Often, patients' awareness of their medical diagnosis is governed by the explanation provided, or the lack of it, by their healthcare professionals. Additionally, the explanation provided also directly influences patients' perceived knowledge, their views on the term CKD as well as the perceived knowledge gap. In general, effective doctor-patient communication is believed to correlate with improved patient health outcomes (437). However, a cross-sectional study showed that CKD discussions occurred only in approximately a quarter of consultations between patients with hypertension and their GPs (438). A focus group study by Crinson et al highlighted reluctance amongst some GPs to embrace the CKD label and their perceived difficulty in explaining the concept to patients (439). In a qualitative interview study of GPs and practice nurses in the U.K., Blakeman et al also reported a predominant theme of anxiety about disclosure of early-stage CKD to patients (440). Similarly, the patients' narrative accounts in another qualitative interview study reflected limited or partial disclosure of CKD diagnosis in the primary care setting (441). Findings from this interview study coincided with those previous studies as unawareness of CKD diagnosis was a recurring issue observed during data collection and at times, posed significant challenges to exploring CKD perceptions and barriers to CKD research.

Though CKD is defined and globally accepted by healthcare professionals as 'kidney damage or eGFR <60 mL/min/1.73 $m^2$ for three months or more, irrespective of cause' (13), many patients have not encountered, understood or agreed with the term or its definition. While some patients were not even aware of their kidney function being checked during their routine blood test or informed of the lowered eGFR readings, the lack of awareness also seemed to be fuelled by the omission of the term CKD by the healthcare professionals when explaining the kidney condition. There appeared to be a tendency for GPs to substitute 'CKD' with descriptions such as, 'slight failing of the kidney' or 'slightly reduced kidney function'. This tendency was certainly not confined to primary care as some who were managed in secondary care for their kidney conditions appeared to portray similar levels of awareness and experience. As a consequence, an interesting discrepancy between patients' knowledge of 'slight reduction of their kidney functions' and their awareness of the diagnosis of 'chronic kidney disease' was observed in some of the interviewees. This disjointed awareness of having a kidney condition was epitomised by one of the interviewees who clearly rejected the diagnosis of CKD despite knowing that he only has one functioning kidney due to kidney stones.

Given that some of the patients were in fact aware of their kidney function being 'slightly reduced' but unaware of the CKD diagnosis label, how should patients' illness awareness of kidney disease be defined? Is awareness of having 'slightly reduced kidney function' adequate or should healthcare professionals be more insistent on patients' awareness of the diagnosis label of 'chronic kidney disease'? Ultimately, does the label of 'chronic kidney disease' matter?

The STOP-CKD research invitation unwittingly created an unusual scenario in challenging patients' awareness of their diagnosis. Patients were informed of their lowered kidney function and possibly the diagnosis of CKD in the research letter. This 'new information' challenged both the patients who were completely unaware of their kidney condition as well as those who had been informed and reassured of their 'slightly reduced kidney function'. Amongst the emergent themes, patients' views about the term 'CKD' provide valuable insight into understanding the disjointed illness awareness among the patients. Intriguingly, irrespective of their overall illness perceptions of a kidney condition, patients perceived the term 'CKD' as a severe, advanced form of kidney condition, which they invariably associated with significant illness consequences. It appeared that patients' lack of awareness of their CKD diagnosis often attributed to their misconception of the term. As the majority only encountered the term CKD via the research invitation letter and had no prior explanation by a healthcare professional regarding the meaning of such a diagnostic label, many 'borrowed' the commonly known illness consequence of severe renal failure requiring dialysis to construct their illness representation of 'chronic kidney disease'. Hence, the majority were unable to reconcile this 'CKD' label with their current health state or the reassuring explanation that they had received from their GPs previously. This did not only result in the discrepancy in illness awareness as mentioned above, but also invariably triggered negative emotional response.

Leventhal's proposed five domains of illness representation provide a useful framework to further examine this issue (268). Instead of representing the illness timeline, 'chronic' was perceived by some to denote severe or advanced illness consequences. Even among some who had the correct understanding, the word

‘chronic’ still triggered an ‘alarmed’ emotional response as they perceived the condition to be incurable. Moreover, some patients also associated ‘kidney disease’ with ‘kidney failure’, therefore related that to severe illness identity, serious illness consequence and even death. This association with death implied their perceived lack of control regarding the condition. Remarkably, despite being given the explanation and correct definition of the medical term by the researcher, many interviewees suggested alternative terms to replace CKD by excluding the word ‘chronic’ or substituting it with words which indicate the severity of illness. It seemed that when given the choice to formulate a diagnostic label, patients prioritised description of illness consequence over description of illness timeline. Though there has been a clear, agreed classification of different stages of CKD since 2003 (19), most patients are not aware of or fully understand what the numerical staging signifies.

Judging from the data that emerged from the patients’ perception of the term CKD, one might now assume that the disjointed illness awareness is simply due to the difference in the perceived illness consequence between the two terms (i.e.: CKD or ‘reduced kidney function’). Nonetheless, it did not appear to be the case. In fact, there was a puzzling mismatch between patients’ emotional response and perceived illness consequence in regards to the term ‘reduced kidney function’. Though patients interviewed in this study were often not aware of other important functions of the kidneys, most had good level of basic knowledge regarding the excretory function of the kidneys which is crucial in sustaining life. Hence, when asked about the consequence of ‘reduced kidney function’, most believed it to be catastrophic and life-threatening. This instinctive association of ‘reduced kidney function’ with ‘complete loss of kidney function’, similar to their perception of the term ‘CKD’, was

an unexpected and contradictory finding as there appeared to be a mismatch between such perceived illness consequences and their emotion reaction. It could be presumed that patients who continued to hold this negative illness consequence view on 'reduced kidney function' would have unvaryingly triggered a negative emotional response when they were first informed of this issue despite the reassurance from GPs. Alternatively, if they had accepted the explanation and reassurance from the GPs, their perception regarding the illness consequences of 'reduced kidney function' should have been moderated, become less severe or more akin to their current state of health (that is, mostly asymptomatic). Yet, these two beliefs had somehow been kept intact but completely disconnected from each another. What is worth emphasizing is that their emotional response to such a diagnosis appeared to be more closely governed by the explanation provided by the GPs than their perceived knowledge. This observation suggested that patients' emotional reaction towards diagnosis disclosure might therefore be less affected by the term used (i.e. CKD or 'reduced kidney function'), but mostly influenced by the ensuing details given regarding the diagnosis' implications. Such finding clearly warrants further exploration in future studies.

Several studies have highlighted the issue concerning the limited knowledge of CKD among the general public (432, 442, 443). Despite being at considerably high risk of developing the condition, a large study of patients with diabetes showed that the majority were unaware of the risk factors associated with kidney disease (444). Even amongst patients with CKD under the care of a nephrologist, Finkelstein et al reported dismal results whereby a third perceived limited or no understanding of their CKD and were unaware of their treatment options (445). In addition, another U.S.-based

study of 399 patients with non-dialysis-dependent CKD, demonstrated that patients felt they have no or limited knowledge in areas regarding 'medications that help the kidney', 'medications that hurt the kidney', 'foods that should be avoided if a person has low kidney function' and 'symptoms of CKD' (446). Older age and higher eGFR were found to be associated with less overall perceived knowledge (446). Furthermore, the same study also highlighted the important discrepancy that existed between patients' perceived and objective knowledge (446). As one of the emergent themes, understanding patients' perceived knowledge gap provides an additional, valuable angle to evaluate patients' illness perceptions of CKD. Similar to the findings from previous studies, the majority of the patients interviewed identified several knowledge gaps regarding CKD, including those who have previously received an explanation from their GPs, though it might also be plausible that the interview process intensified patients' anxiety about kidney disease. The areas of knowledge gaps highlighted were cause and severity of their kidney condition, lifestyle and diet advice, symptoms related to CKD, prognosis and long-term implications of CKD.

Amongst patients who had been informed of their kidney condition, the interview data demonstrated variation in patients' perceived explanation given regarding their kidney diagnosis. GPs' attitudes and beliefs about CKD diagnosis invariably cascaded down to the patients. One such example was relating to the accuracy of eGFR. Although MDRD derived eGFR is a widely accepted method in defining CKD, issues regarding its accuracy and its variability, particularly in the early stages, have been one of the concerns among the GPs (447). The description of the eGFR test as 'a nuisance' by a GP as reported by one patient suggested GPs' uncertainty regarding how the result of

the eGFR should be interpreted. Such comment was likely to have confused the patients and potentially affected the patient's perception of the condition. Interestingly, not all GPs were negative with regards to the variability of the eGFR results as others used it as a reassuring feature and suggested to patients not to be too concerned by a single lower reading on their eGFR result.

Though the cause of CKD was often not explained to the patients, when it was, the majority were told that that advancing age was the reason for 'reduced kidney function'. Understanding the cause of illness is crucial for patients and it embodies one of the five cognitive domains of illness representations (268). While it is a well-known fact that eGFR declines with age (448) and prevalence of CKD increases in the older population (449), a previous study reported high variability in the rate of eGFR decline among individuals (450). In fact, around a third of patients showed no absolute decline in renal function in a longitudinal study (450). Hence, attribution of declining eGFR as just part of the normal physiological ageing process remains a contentious subject (451, 452). Furthermore, lower eGFR was reported to be independently associated with higher mortality across all ages (453), suggesting that regardless of age, reduced eGFR is most likely to be of clinical significance. This is in contrast to the brief explanations patients recalled receiving from their GPs whereby emphasis was frequently placed on reassuring patients that the finding was of no particular significance. Such GPs' effort to reassure the patients was the predominant feature of the theme, and resonated with the findings of a recent qualitative study by Daker-White et al, which reported that disclosure of CKD diagnosis was limited or partial and often cast in vague terms as 'nothing to worry about' (441).

While patients with early to moderate CKD are often asymptomatic, many patients were unaware of such a fact. Indeed, a quantitative study evaluating the usability of the illness perception questionnaire (IPQ-R) highlighted the issue with uncertainty in 'illness identity' in early stage CKD (264), which was echoed by this interview study. The 'rule of symmetry' proposed by Cameron et al appeared to come into play as some of the interviewees felt the pressure to haphazardly attribute any abstract or concrete symptoms they were experiencing to the condition in order to formulate a more tangible illness representation (268). In general, illness identity and illness consequence provide evidence for the existence of the conditions and act as the anchor for illness representations. This sense of uncertainty therefore surfaced and intensified when patients were probed about the impact CKD had on their daily life. Furthermore, disease severity was highlighted to be an important component of the CKD diagnostic label among the interviewees. Belief in more severe illness consequences was shown to be associated with worse outcomes in studies of other chronic illnesses (454-456). Contrary to patients' perception of the consequences of early or moderate stage CKD, large epidemiological studies have long established the fact that the risk of progression to ESRD requiring dialysis among early or moderate stage CKD is low, however, the risk of CV disease is substantial (2, 41, 457). Therefore, it is paramount that these misconceptions and knowledge gaps regarding short- and long-term implications of having CKD among the patients are fully addressed and corrected.

Despite the trivialisation of the CKD diagnosis and fervent reassurance by healthcare professionals, there was nonetheless a prevailing sense of lack of control among some of the interviewees as they were either unaware of the cause of their kidney condition

or were often informed by their healthcare professionals that their kidney condition was simply part of an ageing process. Patients' request for lifestyle or diet advice perhaps symbolised their wish to establish a certain degree of illness control. Previous quantitative studies of other chronic illnesses demonstrated that better perceived personal control over the illnesses were associated with better functioning and more positive mood (258, 458-460). Likewise, Lacroix et al also demonstrated that well-informed patients with a chronic respiratory condition had better outcomes on physical, psychological and social functioning (461). Discussions regarding active self- or pharmacological management of other comorbidities, for instance, hypertension or hypercholesterolaemia, to reduce their CV risk were also often missed during the consultation with their GPs (438). These issues of over-focusing on laboratory findings and overlooking of CKD cause and risk factor management by the healthcare professionals during the explanation of CKD to the patients (438) clearly need to be addressed.

While the common-sense self-regulatory model of illness and health behaviour proposed by Leventhal et al aid the understanding of illness representations, in this interview study of patients with early or moderate CKD, patients' perceptions of their illness were shown to be predominantly shaped by their awareness, explanation provided, emotional response, perceived knowledge, views on the term CKD as well as perceived knowledge gap. The multiple, often bi-directional interactions observed among these six key themes appeared to be crucial in providing the explanations of the varying CKD perceptions amongst the patients. In contrast to Leventhal's model, the CKD illness perception model which emerged from this study highlighted the unique issues with disintegration of illness awareness, uncertainty of illness identity

and mismatch between emotional response and presumed illness consequence amongst this group of patients with early to moderate CKD. These distinctive issues pertinent to patients with early to moderate stage CKD might not only affect patients' illness perception, but might also contribute to their coping mechanism and clinical outcomes as well as their participations in CKD research studies.

In general, though strictly defining patients' awareness of the condition by their recognition of the disease label is probably unwise, the findings from this study suggested that there is a perhaps a justified need to improve the disclosure of the CKD diagnosis by healthcare professionals to the patients. Although there have been concerns amongst some of the healthcare professionals regarding over-burdening patients with CKD diagnosis, especially in its early stage when it is asymptomatic (439, 440, 462), such failure or incomplete disclosure patients' true state of health is a nonetheless a risky paternalistic approach which obliterates the prospect of implementing 'shared decision making' (463, 464). While some argue that the CKD definition leads to unnecessarily labelling (462), many more believe that it improves patients' knowledge and care (463).

The data from this interview study demonstrated that non- or partial disclosure of kidney diagnosis led to mismatch of illness awareness and illness consequence, misconception of diagnostic label and ultimately cause undue stress and anxiety to patients. Additionally, this study also suggested that the lack of awareness of a CKD diagnosis formed a significant barrier to CKD research participation (Chapter 7). A diagnostic label does not only define an illness and facilitate communication among the healthcare professionals, it also serves as a key to patients' illness awareness,

enables patients to seek relevant illness information, facilitates correct illness perceptions and empowers patients' self-management. In addition, this agreement on the diagnostic label also represents the first step in improving doctor-patient congruence on illness perceptions and avoiding patients' negative emotional response when they encounter such a label later in the course of their illness. Indeed, invitations to participate in research bearing the diagnostic label in the STOP-CKD RCT had been shown to trigger significant stress and worries not only amongst those who were completely unaware of their kidney condition, but also in those who had previously received limited or partial disclosure of their diagnosis. Improving patients' awareness of diagnostic label allows them to recognise research studies which are relevant to their own health, and therefore enable them to make informed decision regarding research participations.

### 6.7.1 Implications for Practice and Research

Despite the limitations regarding the lack of diversity in age and ethnicity of the patients interviewed, the findings from this interview study suggest that there is a need to improve public awareness and knowledge of CKD, encourage healthcare professionals in disclosing the CKD diagnosis and ensure shared decision making. This study highlighted the importance of disclosure of CKD diagnosis in improving patients' illness perceptions, avoiding misconception, minimizing unnecessary stress amongst the patients as well as reducing barriers to CKD research.

The seeming over-emphasis on reassurance by healthcare professionals should perhaps be moderated and followed-up with additional information to improve patients' understanding of the condition and reduce uncertainty in their illness

identity. Educating patients regarding the lack of concrete disease identity in early or moderate stage CKD and highlighting the potential red-flag symptoms associated with deterioration of their kidney condition might therefore facilitate patients' self-regulation of their illness perception. In addition, as improved patient-doctor congruence on illness 'identity' and 'cause' have been shown to be associated with illness outcome in previous quantitative study, this crucial information might also help to improve patients' coping strategy and outcomes (258). As patients appeared to value the distinction between early stage kidney disease and ESRD with regards to the disease label, incorporation of the staging classification during explanations of the CKD diagnosis by the healthcare professionals might also be valuable. Other areas of patients' perceived knowledge gaps highlighted also included lifestyle and diet advice, prognosis and long-term implications of CKD, especially in terms of increased CV risk. It is therefore paramount that these misconceptions and knowledge gaps regarding short- and long-term implications of having CKD among the patients are addressed and corrected during diagnosis disclosure and follow-up consultations.

While CKD is not a curable condition and ageing is clearly an inevitable process, provision of advice on self-management and optimising the treatment of other associated co-morbidities might not only influence clinical outcomes, but also be empowering for patients, improving their illness perceptions as well as coping mechanisms by enhancing their perceived illness control. Future research to assess the impact of improved healthcare professional-patient communication on patients' illness awareness, perceptions and experience as well as research participation is clearly warranted.

# CHAPTER 7 FACTORS INFLUENCING RESEARCH PARTICIPATION IN PATIENTS WITH EARLY TO MODERATE CHRONIC KIDNEY DISEASE

## 7.1 Introduction

Despite the potential of clinical research to advance medical treatments, poor recruitment, as faced by the STOP-CKD RCT, is regrettably a chronic and ubiquitous issue. The increasing cost of studies combined with declining funding, lack of motivation and growing responsibilities for clinical researchers, negative perception of industry and suboptimal distribution models for trial finances are all problems for clinical research in general (465). Furthermore, a recent report discussing the challenges faced by the conduct of clinical trials in the United States also highlighted problem with poor enrollment and retention of research participants (465). Indeed, nearly one in five of phase 2 and 3 interventional clinical trials were reported to have either terminated early due to failure to recruit or achieved less than 85% of the initial planned sample size (466). Additionally, a previous survey of authors of published primary care RCTs in the UK also estimated that less than one-third of the studies recruited to their original timescale (467). Poor recruitment does not only gravely compromise the power of the studies in addressing the relevant research questions; it also has strong implications on the time and financial resources as well as opportunities lost among the research participants, investigators, sponsors and the funders.

Though altruism, perception of personal benefit and belief of the importance of clinical trials are a few of the various factors cited as the key motivators for research

participation (468-472), numerous barriers clearly remain and continue to hamper trial recruitment. A detailed literature summary performed by Lovato et al almost two decades ago concerning this issue emphasized the importance of having an overall recruitment plan, the identification and elimination of barriers to recruitment, development of further logistical recruitment strategies as well as recognition of specific recruitment problems in certain disease entities (473). In fact, in a recent priority setting exercise, 'research into methods to boost recruitment in trials' was regarded to be the top priority for trial methodological research amongst the directors of UK Clinical Research Collaboration Registered Clinical Trials Units (474).

Thus far, several characteristics of research studies including earlier phase trials, non-industrial funded trials, fewer number of research sites, non-placebo comparator, higher number of eligibility criteria and trials with 80% power (compared to 90% power) have been quantitatively identified to be associated with less successful accrual (466, 475). From the patients' perspective, fear, worry due to uncertainty, distrust in medical research, lack of understanding of clinical trial process, unwillingness to be randomised due to preference of treatment, side effects of trial intervention, difficulty with informed consent as well as issues with transportation, time and work commitment were highlighted as the common barriers for potential research participants (473, 476-478). Additionally, frequency and total number of research appointments as well as procedure, trial duration, accessibility of study location and physical discomfort associated with procedures were also reported to influence patients' participation (477, 479). Interestingly, a recent qualitative evaluation of patients' participation in telephone care management program cited patients' lack of perceived need as one of the most common barriers (480).

Understanding patients' attitudes towards research participation is clearly an important first step in formulating strategies to improve recruitment. However, the majority of the studies exploring this issue were often not derived from the UK population and predominantly focused on cancer trials (481). Furthermore, none has examined the potential problems associated with RCT trial recruitment which are unique and pertinent to patients with CKD managed in the primary care.

A qualitative study embedded within the STOP-CKD pilot RCT therefore aimed to explore patients' decision-making process concerning interventional CKD research participation in primary care and to identify barriers to recruitment. This was planned with a future larger hard end-point study in mind. However, the failure of STOP-CKD to recruit patients meant such a study could provide some insights into why this had happened. Building on the findings of patients' perception on early to moderate stage CKD detailed in the previous chapter, this chapter presents and discusses the qualitative outcomes of patients' perceived motivators for and barriers to CKD research participation as well as their views on inclusion of elderly patients in clinical trials.

## 7.2 **Methodology**

The characteristics of the 17 interviewed patients, methods of data collection and data analysis were described in detail in the previous chapter (section 6.2, 6.3 & 6.4). Their involvement in the STOP-CKD RCT varied: two patients were enrolled into the RCT; one had withdrawn from the RCT; one was waiting for a screening appointment;

seven were ineligible for the RCT while six declined RCT participation but agreed to be interviewed.

After exploring their perceptions of CKD, all participants were asked about their previous medical research experience, reasons for participation or non-participation in the STOP-CKD RCT, the perceived advantages in taking part in research and disadvantages or barriers to research participations. Further questions regarding their suggestions for future improvement on STOP-CKD RCT study design was also posed during the interviews (Appendix 6-3). During the set-up of the STOP-CKD RCT, one of the recruiting general practices proposed to the STOP-CKD research team to exclude elderly patients above the age of 75 years from the research invitation letters. Conversely, one of the first interviewees voiced her gratitude towards the research team for inviting her to participate in the study despite her being 77 year-old. Therefore, an additional question was incorporated in the topic prompts for the subsequent interviews to explore patients' views on inclusion of elderly participants into clinical trials.

## 7.3 **Results**

The six main themes regarding research participation amongst patients with early to moderate CKD emerged during the interview study. They were (1) past medical research experience; (2) motivators for research participation; (3) barriers to research participation; (4) impact of trial characteristics on research participations; (5) future research suggestions and (6) inclusion of elderly population in clinical trials. These themes provided a useful framework to study the different aspects of patients' views on medical research, especially into CKD in primary care setting. The first theme sets

the scene for exploring participant's attitudes towards medical research based on their previous research experience before moving on to identify the factors which motivated or deterred their participation in research. The fourth theme supplements the second and third themes by examining the influence of certain trial attributes, that is, interventional or non-interventional, primary or secondary care setting, industry or non-industry funded as well as duration or frequency of study visits, on patients' participation in research. In view of the challenges encountered by the STOP-CKD RCT, the fifth and sixth theme gather patients' suggestions to improve future CKD research and their views on the inclusion of elderly population in clinical trials, respectively.

### 7.3.1 Past Medical Research Experience

Before exploring their views on research participation, all patients were questioned on their general experience in medical research studies. Though a few declared no earlier research experiences, most had been involved in various research studies previously. In fact, a number of patients had previously taken part in more than one research study. Based on their descriptions of those studies, most appeared to have been observational in nature, conducted in either primary or secondary care settings. However, during the interview, it emerged that some of the patients might have misunderstood the term 'research' and confused it with being a volunteer patient for the purpose of teaching of medical students.

*"…and I am with that research now if you like. I have been back and sort of how can I put it been a guinea pig for doctors doing their exams etc… at the QE. For them to*

*diagnose what's the matter with me, then to prognosis and diagnosis and prognosis…" Interviewee #15 (declined participation in STOP-CKD RCT)*

In general, patients recalled positive experiences during their previous research participation. The additional medical attention and investigations appeared to have positively enhanced their research experience.

*"I think it is a very, very good thing, and I really mean that, I really and truly mean it. I think it's excellent, hmm… you know, cos obviously I'm going years and years ago, nothing like that ever came, it was only if you didn't feel right and you thought well, it's the doctor I need, or go down…. that was it for whatever you went down for, but obviously these recent years, all the… I think it's a very, very good thing, so…." Interviewee #7 (attended STOP-CKD RCT screening)*

*"Well I enjoyed taking part in it because it was of a particular interest to me and also you know I discovered things when they were doing the various heart things, they look at the heart underneath, at the back, everywhere so you get an idea and somebody said, I said well can I have a look I wanted to see it on the screen which I did." Interviewee #17 (declined participation in STOP-CKD RCT)*

However, despite having enjoyed taking part in research study, the interviewee voiced her frustration as the incidental finding of the investigation she underwent during the research study was not relayed back to her GP in a timely manner.

*"....They said well actually you have got a bit of a leak and I said pardon, you know. Oh well lots of people have small leaks in the heart. So nobody picked up on that at all when those results went back. So as far as I know I don't have a problem.... (*Researcher: *"Did you know the outcome of the study at the end?")…Yes, partly, but I had to ask a lot. Yes, we were told that the results would go back to the GP and I kept asking you know. They said well wait for so many weeks which I did. Eventually, I think they did come back but I know Dr A (patient's GP) had a job to retrieve some. I don't know the reason for that. I just don't...." Interviewee #17*

Additionally, a patient who was a retired nurse at a local hospital also highlighted the interesting observation she made concerning the changes in research regulation and documentation in the past few decades.

*"...We used to get used as guinea pigs occasionally to take bloods at the hospital when they were doing something, 'Can we have a drop of your blood?' when the research registrars were in the hospital... Yes, he was probably doing something and thinks 'I need a drop more blood', so he went around to the nurses and said, 'go on...'... ... Well, they just took the blood and off they went. (Researcher: "Did they get you to sign any consent form?") Oh no, in those days, we are talking in the 80s' and they didn't do things like they do now. (Researcher: "Do you know what they use the blood for?") Not really, no! There were a lot of researches going on AIDS and HIV as they were still learning an awful lot about it.....It wouldn't be set up like yours is now. It's very much on their own back, doing their day job as well as, you know. It's sort of in the side line." Interviewee #3 (attended STOP-CKD RCT screening)*

Interestingly, the presence or absence of previous medical research experience did not appear to directly explain or influence their willingness to participate in the STOP-CKD RCT.

### 7.3.2 Motivators for Research Participation

The reasons for the participation or non-participation of the 17 interviewees in the STOP-CKD RCT could be broadly considered in the three key categories of *altruism, self-interest and perceived relevance of the research topic to personal health*. Other potential facilitators to patients' research participation also included *peer-pressure and awareness of the freedom to withdraw from research participation at any given time*.

#### *7.3.2.1 Altruism*

Altruism is defined as 'disinterested or selfless concern for the well-being of others' (431). Many of the interviewees often conveyed elements of altruism while explaining their reasons for STOP-CKD RCT participation or when describing the advantage of any research participation. In general, their aim was to help others with the illness, help the researchers to find a 'cure' or advance medical knowledge. Awareness of the important role of research in facilitating the advancement of medical science appeared to be a key anchor of this belief.

*"When I first looked, I thought oh god, no, I don't want to do that, don't want to be stuck with needles and stuff like that, and then I thought, no, you've got to join because you know, a lot of people have got the disease and if we all said no, we don't*

*want to do it, how are you ever going to find a cure? Do you know what I mean? I'm not saying you will, but how are you ever going to… it's like cancer, if you don't take things from people how are you going to know how to help people, so that's what I thought. Yeah, if I could do a little bit just to help with research… I mean if we could wave a magic wand and just give us all a tablet and it would all go away, I think everyone would take it, you know what I mean." Interviewee #4 (attended STOP-CKD RCT screening)*

One of the interviewees was clearly aware that her participation in the STOP-CKD RCT might not benefit her health. However, she hoped that her selfless act would reap rewards for the next generation.

*"Because I think the more people that can help in all this research and trials and everything, it might not benefit me at my age but it is possible that it is going to benefit younger people, like my little nieces and other children." Interviewee #13 (awaiting screening visit)*

Another interviewee expressed such 'duty of altruism' elegantly in reply to the reasons for her taking part in the STOP-CKD RCT. Interestingly, as she was asymptomatic from her CKD, her sense of altruism appeared to contain an element of guilt towards the 'less well'. Being a retired nurse, this interviewee's years of exposure to patients' sufferings might have accentuated her empathetic reaction.

*"The fact that you have to find out these things and what happens to me or what my experiences are could help somebody that really needs your help in the future and I*

*think that is what you have to think about. You are well, so let's try to get other people well at the same time. Sounds very pious, you know, you see so many people suffering and you think, you know, I am so well, I don't deserve to be so well really." Interviewee #3 (attended STOP-CKD RCT screening)*

#### *7.3.2.2 Self-interest*

Self-interest featured strongly during the interview in regards to patients' motivation for research participation. Most of the interviewees who were willing to take part in the STOP-CKD RCT indicated that one of the main drivers for their research participation was their perceived personal gain, in the form of increasing personal health knowledge on the specific condition (interviewee #1), having additional health monitoring (interviewee #8) or potentially improving their health status (interviewee #6).

*"Well, the fact that I'd been told I'd got failing kidneys. I thought well, you know, that's what I said to you (turned to his wife), isn't it? I said I'll volunteer myself for this because I'm supposed to have failing kidneys so they could tell me how bad they're failing, or how fast, or quick, or if there's anything I can do to help the situation…" Interviewee #1 (attended STOP-CKD RCT screening)*

*"Well, I don't mind going on any trial because in a way they are monitoring your health really, so I think there are benefits for the patient really …" interviewee #8 (STOP-CKD RCT participant)*

*"I thought it'd probably help me and it would help other people in the survey, cos I read the letter and it said that these tablets are supposed to help, err, that I was obviously taking, of people in hospital. Erm… it's good for their kidneys and they've got something else wrong with them..." Interviewee #6 (withdrawn from STOP-CKD RCT due to adverse event)*

Interestingly, an interviewee self-professed his motive of personal gain as 'selfishness'. This over-riding 'selfishness' seemed to be his primary driver for research participation and appeared to counteract the 'fear' which was often mentioned as the barrier to participation (section 6.3.4).

*"Selfishness. (Researcher: 'In what way?') Well, if I had got a kidney problem, I would rather go and see if I could find some way of solving a problem if that is what it could be. I am not frightened to do it but I have never been asked before. If you would have asked me without me having this identified in my tests, I would have said yes, I would do it, but I am not afraid to go on tests and things like that. It doesn't bother me one little bit. I would quite easily say yes to trials." Interviewee #10 (attended STOP-CKD RCT screening)*

#### *7.3.2.3 Perceived relevance of research topic to personal health*

Perceiving the research topic to be relevant to their own health was often an important prerequisite for perceiving research participation to be of personal gain. It therefore played an important role in driving patients' research participation.

*"...because of the conditions I've got. To put it in a nutshell, if it was a cancer you were researching I wouldn't bother, cos hopefully, touch wood, I haven't got cancer. So that is why I went in because it was things I'd got wrong with me." Interviewee #1 (attended STOP-CKD RCT screening)*

*"... It's monitoring my blood so, you know, and blood pressure which I know is important in terms of my condition. So I am prepared to do that." Interviewee #8 (STOP-CKD RCT participant)*

In fact, another interviewee who elegantly illustrated this similar point demonstrated a key and significant finding from this interview study: patients' acknowledgement of the relevance of the research topic to their own health was the indispensable first step in patients' research participation. Without it, it appeared that patients would be unlikely to participate, even in the presence of other drivers.

*"Yes, because I mean in my case I doubt if I would have volunteered had it not been relevant to my medical, so that's why I suppose, if you're researching a particular thing and attach it somebody's problem, then they're wanna know a bit more and come and see you. " Interviewee #1 (attended STOP-CKD RCT screening)*

#### *7.3.2.4 Peer-pressure*

In addition to the three vital factors mentioned above, there were also several other factors which facilitated research participation. Two of the interviewees were encouraged by their family or friends to take part. Such encouragement appeared to

be based upon self-interest or altruism and reinforced interviewees' willingness to research participation.

*Interviewee #9 (attended STOP-CKD RCT screening): "My husband, wasn't it (turned to husband)? You influenced me to take part in this."*
*Interviewee #9's Husband: "Yeah, I just advised her, thought it would be a good idea – she would be able to contribute to something and also the regular monitoring is not a bad thing either".*

*"I think talking to friends about it and they encouraged me to do it because they thought I had more to gain from it than I was to lose from it." Interviewee #8 (STOP-CKD RCT participant)*

*7.3.2.5 Freedom to withdraw from research study*

Furthermore, awareness of being able to withdraw from the research study at any given time appeared to also help in alleviating the concerns one of the interviewees had with regard to the potential side effects of the trial medication. It seemed to be a reassuring feature, which conceivably provided participants with some degree of perceived control and therefore encouraged their participation.

*"Well, I would have taken part and if it had been making me feel sick, then I would have stopped." Interviewee #9 (attended STOP-CKD RCT screening)*

### 7.3.3 Barriers to Research Participation

The interview study further explored patients' perceived barriers to research studies in relation to the STOP-CKD RCT as well as in general.

#### *7.3.3.1 Perceived lack of relevance of research topic to personal health*

While patients acknowledging the research to be relevant to their personal health was noted to be the fundamental driver of research participation, due to the low level of CKD awareness amongst asymptomatic patients (Chapter 6), research invitations, such as those from the STOP-CKD RCT, unfortunately failed to bear any relevance to the large proportion of its target population and did not appeal to potential participants' self-interest. Such findings evidently echoed those described in Chapter 6 and section 7.3.2. It represented a crucial and unique barrier for research participation pertinent to this group of patients managed in the primary care. This was clearly demonstrated by interviewee #12 who stated personal health gain and advancing medicine as the benefits of research during the interview but her perceived view of the irrelevance of the study took precedence and deterred her from taking part in the STOP-CKD RCT.

> *"Well, if I had wanted to participate for any reason, I would have gone and asked my doctor first. You know, the for and against. I mean I am very much in favour of research and experimentation but I have got nothing wrong with me, so it was not applicable to me." Interviewee #12 (declined to participate in STOP-CKD RCT)*

#### *7.3.3.2 Fear and uncertainty*

Fear was another predominant factor highlighted by the majority of the interviewees as the barrier to research participation. Delving deeper into the core of the issue, there were multiple factors contributing to such fear which emerged during the interview.

Of particular interest was the high level of apprehension noted amongst some of the patients who regarded being invited to participate in research studies as 'bad news'. In addition to the low diagnosis awareness, the term CKD was often perceived to have significant negative connotations amongst the interviewees as discussed in Chapter 6. Therefore, it was perhaps unsurprising that some interviewees expressed strong anxiety upon receiving the invitation which deterred them from participating in the research study.

> *"Well, it's like you know you receive a letter and you think 'oh my god I didn't think I had got anything wrong', you know and then well maybe I should, maybe I shouldn't, what should I do. I think people can be fearful of taking on something new. Hmm… also I think if you do receive something through the post, you may think well, you know why me and it may put people backs up a bit. Hmm… not to be very receptive or well I'm okay now so why should I be bothered…." Interviewee #17 (declined to participate in STOP-CKD RCT)*

Another key driver of the fear appeared to be the lack of control or uncertainty associated with trial medication assignment. The clinical equipoise which fundamentally provides the basis for medical research, and RCTs especially was felt

to be unacceptable for some and represented a significant barrier to participant recruitment.

> *"Well, for example with this one, how would that benefit me? I don't know whether I am, you know, if I decide to take part and swallow the pills, I don't know if they are placebo or if they are a drug..." Interviewee #17 (declined to participate in STOP-CKD RCT)*

In addition to their uncertainty about research participation, which was compounded by the lack of understanding of equipoise in clinical trials with the use of a placebo, one of the interviewees also highlighted the uncertainty of end-of-trial arrangements.

> *"How they are going to react to the tablet and how it's going to leave them once they've finished it, because they are not going to be doing it for ever, so they are going to think 'is something going to happen to me when I stop taking this tablet', because they won't know whether it's the placebo or whether it's the genuine or not, but they won't know if it could make a difference to them later on." Interviewee #3*

Furthermore, descriptions such as 'being used as a guinea pig' also conceptualised public feelings of uncertainty and lack of control of their personal health associated with research studies.

> *"Well, I think some people might think they are using me as a guinea pig and they are trying drugs out or they are trying drugs out on me or they don't quite know the results of them. I think some people might have that feeling behind, you know, you*

*don't want to do that because you know a couple of people I have spoken to said, 'oh no, you don't want to do that'…" Interviewee #16 (declined to participate in STOP-CKD RCT)*

While some of the interviewees believed additional monitoring of their health was an appealing feature of participating in a research study, interestingly, some were afraid of the potential for unexpected incidental findings that might be discovered during the research study.

*"Maybe some people are a bit frightened, you know, when they get the letter, you know they don't wanna know. Hm… whether, you know, they might be afraid…if they find something else, you know, when they go on that study." Interviewee #6 (withdrawn from STOP-CKD RCT due to adverse event)*

*"Because some people fear about their bodies and about death and all the rest of it. They would rather not know… a need to know basis attitude." Interviewee #15 (declined to participate in STOP-CKD RCT)*

Additionally, though some might not necessarily view venepuncture as an invasive procedure, others expressed apprehension about such procedures. Therefore, the frequency and invasiveness of these procedures could potentially affect research recruitment due to the fear patients have about procedures.

*"The only downside of being … is you'd have to keep sticking me with needles…. That's the only thing. You know when you say you have to keep taking blood I'm*

*thinking 'oh god I'm going to be a pincushion'. Because obviously when you go into hospital, 'can we have some more blood, more blood' – oh god, no more! That's the only downside I see." Interviewee #4 (attended STOP-CKD RCT screening)*

#### *7.3.3.3 Free-riding tendency*

In the face of uncertainty, a few of the interviewees believed that some may default to the perceived 'safer' option of not taking part, suggesting a 'free-riding' tendency amongst those who declined to participate. The term 'free-rider' was used to described 'a member of a group who obtains benefits from group membership but does not bear a proportional share of the cost of providing the benefits' (482). This 'free-riding' tendency represents the counterforce of altruism and appeared to be the results of patients' compelling urge to safeguard their self-interest.

*"Only not knowing what it may do to them. That's naivety in a lot of cases, unfortunately. Well, not naivety, that is the wrong word. It is just being probably a little bit scared that it won't do them any good and they will not feel very well and they would rather let somebody else do it." Interviewee #10 (attended STOP-CKD RCT screening)*

*"…They just say well I'm alright at the moment there is nothing wrong with me. They just put it in the background, don't they, a lot of people do, don't they? Instead of thinking well you know it might be helping somebody in the future…" Interviewee #5 (declined to participate in STOP-CKD RCT)*

#### *7.3.3.4 Medication burden and side effects*

Whilst the majority of willing participants interviewed did not view the use of trial medication as a significant barrier, others who declined to participate were vehemently opposed to taking any extra medication when the benefits for themselves were uncertain. The potential side effects of the trial medications or their potential interaction with their existing medication also deterred some from taking part as they felt that the risks clearly outweighed the benefits. Such varied perceptions amongst the interviewees were likely to be influenced by their perceived personal health status, their interpretation of the potential benefits of the interventional medication (spironolactone), as well as their pre-existing medical conditions.

*"For me, because I looked up the side-effects, now I know that the side-effects don't affect everybody and most people probably only have mild side-effects, but I'm just sort of thinking well I am coasting along and I would prefer to stay that way unless a particular problem comes up." Interviewee #17 (declined to participate in STOP-CKD RCT)*

*"Well, this one obviously because of my own kidney problem but I don't want to take any more tablets because I am already on tablets and I don't want anything to stop the good work that is going on at the moment with my eyes (myasthenia gravis) and with you know my blood pressure one. I don't want anything to react so that's why I've said no more tablets." Interviewee #15 (declined to participate in STOP-CKD RCT)*

Furthermore, for those who already take a substantial number of pills, the addition of a further trial medication represented an unwelcome additional load on their already heavy medication burden.

*"... It is just that I don't need to. I don't take anything unless I have got to, you know." Interviewee #12 (declined to participate in STOP-CKD RCT)*

*"No, and I can see also that I don't necessarily need to require a benefit to me. And plenty of people will say, well, maybe it doesn't benefit me but hopefully (it) will benefit people in the future. I can see that but for the time being, I don't wish to swallow tablets in order to prove that, you know." Interviewee #17 (declined to participate in STOP-CKD RCT)*

*7.3.3.5 Pre-existing medical issues*

In addition, patients' pre-existing medical issues also played a role in deciding on research participation.

*"Well, because of this condition (skin rash) I have had. I thought it is no good going on tablets, on placebos or whatever you are supposed to give me... Yes, and the tablets have supposedly caused this. I thought there is no point going on a kidney test. Well you know a trial, until this has cleared up really." Interviewee #5 (declined to participate in STOP-CKD RCT)*

*7.3.3.6 Impact on daily lives and other commitment*

Being the care-giver for a family member also represented a significant barrier to research participation due to the time required for research visits.

> *"...I would have done this you know but there is no point me doing it if I have got the bladder problem (cancer) so ... and ***** (her husband) being poorly as well, although he is a lot better now, the chemo really knocked him about." Interviewee #11 (declined to participate in STOP-CKD RCT)*

With only one exception, all of the interviewees were either retired or not in a full-time job. However, many did recognise time and work commitments as barrier to research participation, especially for working people.

> *"I suppose, if people are at work – if people are doing 9 to 5 that can be difficult. See I work shifts, so it's a bit better for me, but if you're doing 9 to 5 it's difficult for people to fit it in." Interviewee #4 (attended STOP-CKD screening)*

Another interviewee also expressed the possible issue with the intrusiveness of research participation on daily life.

> *"The cons ... I suppose the cons can be it can invade your life too much, I suppose, if you allowed it to. You know you might not want to be called on too much and you didn't want to do it." Interviewee #15 (declined to participate in STOP-CKD RCT)*

### 7.3.4 Pathway Leading to CKD Research Participation

The relationship among the key motivators and barriers to patients' participation in research are presented in Figure 7-1. Patients' decisions whether to participate in the research study appeared to be primarily dependent on the balance between these factors. Above all, the perceived relevance of research topic to patients' own health, or the lack of it, emerged as the crucial factors governing such decision amongst interviewees. Such perceptions were also closely linked to their self-interest as detailed in section 7.3.2.3.

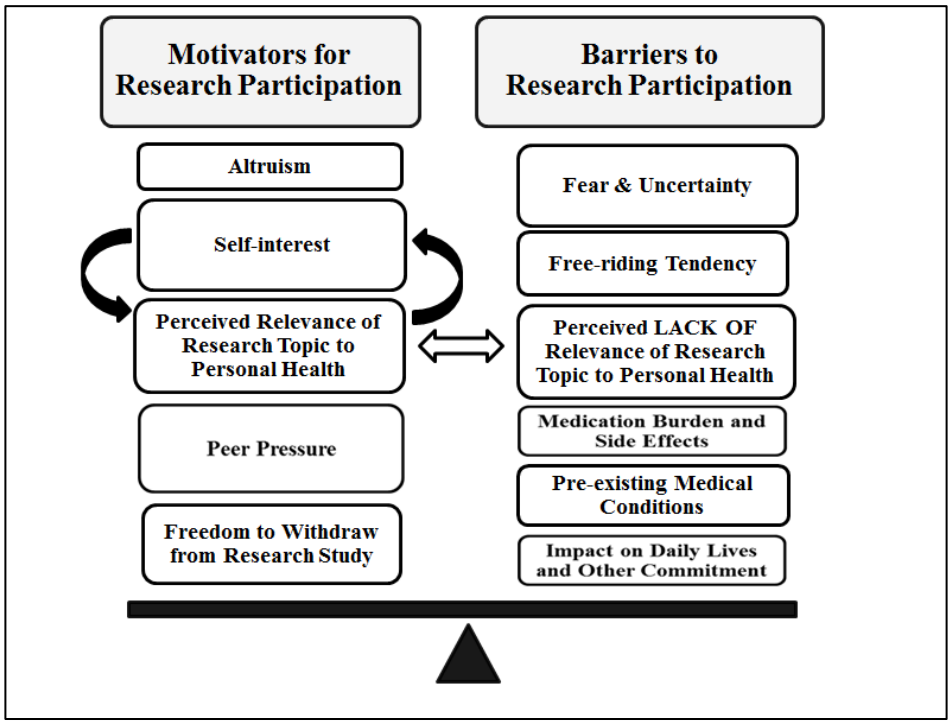



Figure 7-1: Key factors which influence patients' research participation.

The health belief model, which consists of four main dimensions: perceived susceptibility, perceived severity, perceived benefits and perceived barriers, has been widely used in explaining and predicting health-related behaviour since early 1950

(483). Perceived susceptibility was reported to be a more influential factor than perceived benefits in understanding preventive health behaviour while the reverse was the case in the understanding of sick role behaviour (483). Additionally, internal (i.e. symptoms) or external (i.e. interpersonal interactions) 'cues to action' were believed to be vital in triggering the decision-making process (483).

Employing the concept of the health belief model (483), Figure 7-2 illustrates and summarises a conceivable linear pathway leading to CKD research participation. The pathway consists of three crucial links of patients' perceived susceptibility, perceived severity and self-interest. The perceived relevance of the research topic to personal health was the key to initiate the pathway as without this fundamental belief about susceptibility, patients would be unlikely to consider research participation. Provided that patients accept their diagnosis of CKD, the perceived severity and hence the consequence of the illness appeared to be the next crucial step when deliberating their participation in an interventional study. The evaluation of the multiple factors relating to the pros and cons of participation, as discussed earlier, subsequently came into play once the susceptibility and severity of the illness were acknowledged. Maintaining a 'net personal gain' and safeguarding their individual self-interest were found to be major factors in prompting research participation. Though altruism is often cited to be a major motivator for research participation, the findings of this interview study suggested that its role is perhaps much less important than the maintenance of self-interest. 'Peer-pressure' and awareness of the 'freedom to withdraw from research' potentially act as the 'cues to action'. As research-active GP sites appeared to have a statistically significantly greater recruitment rate compared to their counterparts (see

Chapter 5), it is conceivable that such effect might have been mediated via the 'perceived benefits' or 'cues to action'.

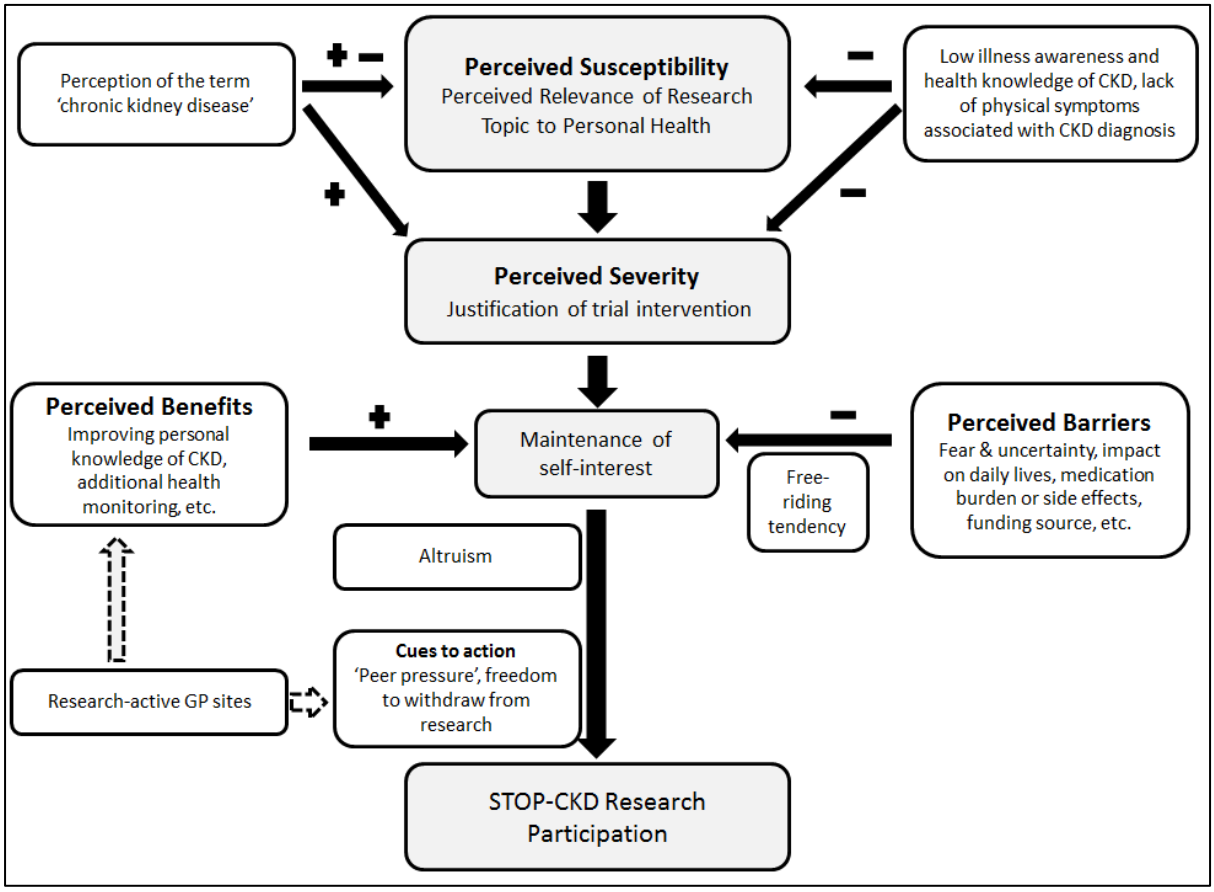



Figure 7-2: Modified health belief model illustrating the pathway of patients' decision in the STOP-CKD RCT research participation.

### 7.3.5 Impact of Trial Characteristics on Research Participation

In addition to examining the key factors which influenced their decisions in participating in the STOP-CKD RCT, interviewees were also asked specifically regarding the impact certain study attributes, for instance, trial intervention, trial setting (primary or secondary care), funding source and frequency or duration of study visits might have on their decision to participate in any research study.

*7.3.5.1 Trial Intervention*

In general, the majority of the interviewees stated that they were not deterred by studies involving trial medications. Patients' trust in researchers appeared to be fundamental to their willingness to participate in interventional studies. A well-controlled study which involved only a low-dosage, once daily regime of a trial medication, like the STOP-CKD RCT, were reassuring features for one of the interviewees.

*"As long as it's well controlled and it's not being given to you in a massive dose so that it is only like a little test to see how you respond or how the body reacts to it, it's got to be well looked after." Interviewee #3 (attended STOP-CKD RCT screening)*

Although the serious side effects of low-dose spironolactone are infrequent and common side effects are often mild, the STOP-CKD RCT patients' information sheet clearly listed the potential side effects to ensure all participants were well-informed of the risks involved. One of the willing participants of the STOP-CKD RCT seemed to have underplayed the risks and was not concerned about taking part in an interventional study.

*"It didn't scare me because, as I say, you said one was gonna be nothing so I knew that if it was nothing, it was just going to be a vitamin, or something silly like that, and I knew the other would be a water tablet. So knew it wasn't gonna do…. I just knew if I'd got the water tablet I'd go to the toilet more often, but apart from that I wasn't too worried. I knew it wasn't something that was gonna to affect my heart, liver or anything like that…..I just knew it was gonna…… you know, I know a lot of*

*people who are on water tablets – I mean I'm on water tablets now. I know it doesn't affect them at all, just obviously more trips to the bathroom." Interviewee #4 (attended STOP-CKD RCT screening)*

In contrast, whilst another interviewee also did not view trials involving pharmacological intervention as a barrier to participation, it was based on the condition that the trial would not interfere with his existing medications and that the trial intervention had a substantially high benefit to risk ratio.

*Providing the trial medication… providing you would tell me what it's for – if it is to improve my kidney function, that's fine, I can accept that over even the real medication, or the placebo – it wouldn't make any difference because then in the end you would say it either works or it doesn't work. You are the ones who would have all the knowledge. That's it. It's got to be beneficial to me, but not detrimental, that I'd have to substitute a placebo for my original medication. Like, can you understand? Interviewee #2 (attended STOP-CKD RCT screening)*

However, for another interviewee, despite stating that she would not mind taking part in an interventional study as long as it was not too radical, for instance, a surgical operation, she declined to take part in the STOP-CKD RCT as she felt that trial medication might worsen her symptoms associated with over-active bladder. This highlighted the fact that although the majority of the interviewees did not state any apparent strong objection against interventional studies, they were unlikely to take part in the research if the studies did not appeal to their self-interest.

*"...There was only this one with the tablets that put me off. I mean if the tablet had not been a water tablet I might have gone for it but I thought well that is just the opposite to what I need really. .. Yes, I have what they think is an over-active bladder and I do keep getting recurring urinary tract infections quite often really, so much so that the doctor did put me on an antibiotic just one low dosage one daily to try and keep it at bay..." Interviewee #16 (declined to participate in STOP-CKD RCT)*

For some, they simply had a strong aversion towards taking additional tablets or concerns about the potential side effects and therefore would not participate in interventional studies (section 7.3.3.4).

*"I would not be in favour of taking something if I didn't need it or wasn't told to for a reason from the doctor, I wouldn't do that." Interviewee #12 (declined to participate in STOP-CKD RCT)*

#### *7.3.5.2 Trial Setting*

In addition, interviewees were also asked if they had any preference for research conducted in primary or secondary care settings. While some had no preference, others generally preferred the convenience of a shorter travelling time as well as the free parking available to the primary care-based research studies. Another interviewee also felt that research conducted in primary care had the advantage of being more personal for the participants.

*"Well, for my personal, I would rather it be done in the doctors surgery, for one thing it is more convenient. See, I don't drive. It is more inconvenient to get to the hospital*

*and I think it is possibly a bit more personal in your doctors' surgery than going to a big hospital." Interviewee #16 (declined to participate in STOP-CKD RCT)*

*7.3.5.3 Funding Source*

There were diverging opinions and views in terms of the funding source for research studies. Several interviewees expressed no preference about the funding source provided the research helps to advance medical science. Poignantly, against the backdrop of the financial challenge faced by the NHS, an interviewee's wife who was present during the interview also alluded to the fact the government is unlikely to be able to fund all medical research studies without the help of pharmaceutical companies.

*"... now, if it's good for people's health, I don't care where the money comes from (laughing)." Interviewee #1 (attended STOP-CKD RCT screening)*

*"Well, the pharmaceutical companies are bound to want to fund it and I can't imagine that the NHS would have the funding to do it all, they just wouldn't. So there has got to be the balance between, you know the NHS and the drug companies and drug companies obviously provide a lot of research which is always going to be needed for any drug." Wife of Interviewee #5 (declined to participate in STOP-CKD RCT)*

A similar opinion was voiced by another interviewee as she witnessed the contributions pharmaceutical companies made in advancing medical treatment. Nonetheless, there was still an element of guardedness towards the pharmaceutical

industries and it appeared that she would only participate in industry-funded research if their trial design stood up to her scrutiny.

*"No, but I'd like to think that if it is a drug company, that you are not going to just abide by what they do or their drugs because others might be just as efficient, so until you know that you can't make a decision, but no, I think drug companies have got to do this to be able to create new drugs and that's how we've got so many new drugs these days is because the research was done years ago… It's usually drugs isn't it? The government haven't got the cash these days to be able to fund things. If they have the money to do it, then fair enough. There are an awful lot of things that need our government money nowadays." Interviewee #3 (attended STOP-CKD RCT screening)*

Nevertheless, not all of the interviewees were impartial about pharmaceutical company funded studies. One of the interviewee associated such research with that of the disastrous first-in human drug trial in Northwick Park, which was extensively covered and heavily criticised by the media in 2006 (484).

*"I don't know, because the private one … I don't know, because you remember those gentlemen a few years ago, you think straight away when they had theirs and obviously it all went wrong, sometimes you think, hmm… you know, but you didn't hear the story of what they were going…" Interviewee #4 (attended STOP-CKD RCT screening)*

Several of the interviewees expressed strong preference for government funded research studies as they were wary that the primary intention of the pharmaceutical companies might be of financial rather than patient benefit.

*"Well, I have a horrible feeling that it is the money that kind of triggers the whole thing and it may not altogether be in the interest of the patient but you know may be I'm wrong in that but I do have that sort of feeling." Interviewee #17 (declined to participate in STOP-CKD RCT)*

*"To some degree I suppose. I think possibly if you are thinking you are promoting the drug company's profits you might have a bit of an issue with it. I think if it is the medical profession as a whole and the government is trying to see the best way of treating a certain area, then I think if people realise that then they would be more than willing to be helpful in this." Interviewee #16 (declined to participate in STOP-CKD RCT)*

Despite having limited financial resources, one interviewee stated that the government should increase their financial support, in a timelier manner, for research studies of common medical conditions.

*"My only view is that I think the government should do a little bit more for you definitely. I know that they are saying this morning on the TV; they are going to do a lot more now for Alzheimer's disease and allow more money for it, which actually should have been done a long time ago and the same with kidneys really." Interviewee #16 (declined to participate in STOP-CKD RCT)*

#### *7.3.5.4 Duration or Frequency of Study Visits*

In regards to the duration or frequency of research visits for the STOP-CKD RCT, most did not perceive either as barriers for participation. Two of the interviewees felt that they had the time to do so whilst another interviewee was reassured that the research visit could be fitted around her working hours.

> *"That didn't bother me as long as obviously you know you didn't mind that obviously I had to fit it in around work, which was quite OK as the lady said if you know, you've got to do it through work, around work, that was fine and I was happy with that." Interviewee #4 (attended STOP-CKD RCT screening)*

Nonetheless, there was one who preferred to have less frequent visits to avoid disrupting his daily routine and another suggested 'research-fatigue' might occur with studies that have a longer follow-up period.

> *"Yes, 3 or 4 months (frequency of visit). Well, or even longer if necessary but certainly no shorter because I would have to keep planning my life around that appointment." Interviewee #15 (declined to participate in STOP-CKD RCT)*
>
> *"... I suppose if it goes on for a long, long while you might get a bit tired of it but I mean sometimes these things do take time don't they." Interviewee #16 (declined to participate in STOP-CKD RCT)*

### 7.3.6 Future Research Suggestions

Overall, most of the interviewees who were screened or participated in the STOP-CKD RCT found the research experience to be acceptable. The majority of the interviewees agreed that the patient information sheet for the STOP-CKD RCT was informative and helpful.

> *"Yeah, really informative – it tells you all about what's going to happen, what you're going to do and there was a number if I wanted to chat to anybody." Interviewee #4 (attended STOP-CKD RCT screening)*

However, a few of the participants highlighted a few concerns regarding the discomfort of the simultaneous blood pressure measurements on both arms and the quantity of the blood taken.

> *"Well, yeah, having both arms at the same time. It wasn't a problem standing up but you had to have them done stood up. I mean the blood, it was six syringes of blood, but you know, there you go, as long as you can spare it (laughing)!" Interviewee #1 (attended STOP-CKD RCT screening)*

In addition, one of the patients also criticised the repetitive paperwork associated with the STOP-CKD study and wondered if such defensive method of research conduct were due to the researchers' fear of potential legal repercussion.

> "*… There is a lot of repetitiveness in it. Like that sheet (consent form) there I've four already, four or five of those already. I have sent some back. I have signed during*

*the… and again. That it is why it did not take me long to read it. That doesn't bother me that much; it is just whether you are repeating yourself too many times in certain areas. It is almost as if you are frightened that you don't get the consent of the person, there will be some comeback to you." Interviewee #10 (attended STOP-CKD RCT screening)*

A number of interviewees made some other constructive suggestions on how the STOP-CKD RCT could potentially improve its design and recruitment. During the screening visit for the STOP-CKD RCT, a questionnaire regarding participants' demographics and medical history was completed before the research team proceeded to measure their blood pressure. An unexpectedly large proportion of the participants were found to be ineligible for the study due to low blood pressure. Hence, an interviewee suggested that the blood pressure could be measured first to identify eligible participants before completing the questionnaire.

*"…It was to the point, asked me the questions and then …… I didn't need to have blood taken because my…. I wonder why they didn't just take my blood pressure at the start, it would have saved a lot of questions, wouldn't it? So my god, we've given him loads of forms to fill in, and now it's no good." Interviewee #2 (attended STOP-CKD RCT screening)*

Additionally, the same interviewee also suggested that invitation letters should be more reassuringly worded to avoid triggering fear amongst the recipients. In parallel with the findings in Chapter 6, as the awareness of mild to moderate CKD diagnosis amongst the patients in the community is low (7), many appeared to be taken aback

by the suggestion of their diagnosis of reduced kidney function or CKD on the research invitation letter.

*"I think the wording could be processed better – 'this is nothing to be alarmed about'." Interviewee #2 (attended STOP-CKD RCT screening)*

*"I think what really surprised me was the chronic kidney function (failure), I think you know nobody has told me that I didn't know whether there was anything I could do to help put it right but nobody had suggested there was a problem and I think that is why I thought I didn't know that." Interviewee #16 (declined to participate in STOP-CKD RCT)*

As the STOP-CKD RCT faced issues with poor recruitment, this qualitative study also explored interviewees' views on ways to overcome the problem. Instead of a postal invitation, some interviewees felt that a face-to-face approach is more personal and might help to alleviate their fear and rectify any misconceptions they might have regarding the study. One interviewee proposed contacting individual potential participants via telephone but was later concerned regarding the intrusiveness of such approach.

*"Maybe go out and speak to people, like you're doing now, before you call them in to do blood pressure tests and things like that. You put people at ease and they know what is involved instead of sort of sitting reading a leaflet, it might…. I know it's time, and taking your time, and more doctors going out, but nurses could do it and things like that, couldn't they? You know. I think, as I say, communication, putting people at*

*ease, because people get frightened when they don't know what's what, or what's happening, and information…hmm, seriously, yeah – I think so anyway." Interviewee #9 (attended STOP-CKD RCT screening)*

*"I think the person to person approach is always better than stuff through the post frankly and sort of in between that I suppose is an approach by telephone but then that can be intrusive. I think people don't like things that are intrusive generally speaking." Interviewee #17 (declined to participate in STOP-CKD RCT)*

Another interviewee considered research advertisement to be another method of boosting recruitment. Incorporating current participants' positive comments into future research invitation letters was also suggested by another interviewee.

*"Well, at the moment you are doing it just through GPs, aren't you? Yes, there is enough GP health centres, isn't there for people to. I don't know where else you could do it apart from advertising in newspapers I suppose but then it is costly isn't it?" Interviewee #11 (declined to participate in STOP-CKD RCT)*

*"Perhaps you could get a little leaflet out that you send out for people's comments of those taking part so that they know how little time it takes up and how they're not having any reaction to anything, so they've got something to fall back on to say, well, it didn't happen." Interview #3 (attended STOP-CKD RCT screening)*

As time constraints were suggested to be one of the barriers for research participation for working people, an interviewee proposed conducting the research visit in the evening or during weekends.

> *"I suppose people would have to try and come in the evening… Yes, out of normal hours or weekends or something." Interviewee #8 (participant of STOP-CKD RCT)*

Conversely, one of the interviewees appeared sceptical regarding the effectiveness of any of such strategies.

> *"I think it is difficult because people have got to want to and you can't force people. You can lead a horse to water but you can't make them drink. It is like everything if you want to pack smoking up you will, if you want to stop drinking you will, if you go about if half-hearted you won't and so at the end of the day whatever you do you can only advertise it or offer it. You can't make people do it and I think it is up here (pointed to his head) whether people want to do it or not and I don't think whatever you do will make it any more attractive because it can be as attractive as you like but if they don't want to do it, they won't do it." Interviewee #15 (declined to participate in STOP-CKD RCT)*

### 7.3.7 Inclusion of Elderly Participants in Clinical Trials

During the setting up of the STOP-CKD RCT, one of the recruiting sites proposed excluding elderly patients (75 years and above) from being invited to participate, believing that they might be too frail to take part in such an interventional study. Therefore, the interview study took the opportunity to further explore patients' views

on inviting the elderly to participate in research studies. Interestingly, most of the interviewees had dissimilar views to those of the GPs. In fact, one of the interviewees, who was 77 year-old, clearly appreciated being included in the research study and was delighted to have the chance to take part.

*"I think it's very, very good of the doctors that they're interested, at the ages I am, you know, so I think it's extremely good." Interviewee #7 (attended STOP-CKD RCT screening)*

Additionally, many of the interviewees felt that there were several compelling reasons to include participants from all ages and found no clear reason to exclude elderly populations. They believed that age should not be a limiting factor if research is performed for the health benefits of the public and that the condition studied affects people from all ages. As biological functions vary with age, another interviewee also thought that the results found in the selective group of participants of younger ages might therefore not be applicable to those who were older.

*"Well, I suppose everybody's life counts doesn't it? You know, whatever age." Interviewee #5 (declined to participate in STOP-CKD RCT)*

*"I don't think there is any reason why you shouldn't do. I think the thing is every age group is going with various studies type thing is going to show up anomalies in line with various things. I mean some people say only 20/30 or 40's type of thing, they are probably able to more absorb medication whereas a lot of older people may not be, so it could affect them on that basis, so I can't see why anybody shouldn't be, you*

*know, should be exempt from a study. To get a cross-section of people, you need to get a cross-section of ages." Interviewee #14 (STOP-CKD RCT participant)*

*"I can't see why age should be a barrier really. Otherwise you would be saying people above a certain age, there is no point in monitoring people like that because they haven't got long to go or whatever really. I think the condition is universal to age really and the treatment you are thinking of are going to be beneficial to all ages, I don't see why it has to be age discriminating." Interviewee #8 (STOP-CKD RCT participant)*

One of the interviewees also felt that elderly population might be more willing and prepared to help in research, as they might not be as restricted by work or time constraints when compared to younger patients.

*"I think that is a good idea for elderly people to take part in research, definitely. I think the younger generation, they don't realise. They are so full of what is going on in their lives and young mothers becoming pregnant and all that, so the older generation, yes, I think they could do quite a bit actually." Interviewee #11 (declined to participate in STOP-CKD RCT)*

Likewise, one of the interviewees felt passionately that elderly patients should be listened to and believed that their knowledge was valuable for others with similar conditions.

*"I think they should. Absolutely, because I work with the elderly and just because they're elderly, why shouldn't they have a voice? As I say, my lady goes, and she's 75 I think she is, and she goes and she's an elderly lady. I mean, we nurse her in bed but for 2 hours once every 2 weeks I think it is, she goes, sits and chats to people, much, much younger than her, and she gets a lot out of it, so you know, a lot of these elderly people, just because they're frail in body, they've got a good mind, do you know what I mean. I think yeah, they should be involved. And if they've had to live with it for a long, long time, they're the best people to ask aren't they, do you know what I mean, they've been there before us and they will have a lot of knowledge and stuff that I think….. And sometimes they'll give us coping mechanisms that we probably haven't even thought of." Interviewee #4 (attended STOP-CKD RCT screening)*

From a more clinical standpoint, another interviewee felt that by including patients from all ages, it might allow certain epidemiological patterns to emerge and help to guide further research planning.

*"I would have thought it needs to be left open ended really because as you are doing your research, you will get a pattern of where the highest proportion of difficulty is, won't you? So if you say, you may say well after 85, you have got to die of something, I am being slightly frivolous, I am serious really, but you know if it throws up that kind of pattern, that it's not really worth doing a great deal say for people from 90 because they are not going to live very long anyway and you have got to die from something but I would think keep it open ended. I wouldn't want to say a cut off either end really." Interviewee #17 (declined to participate in STOP-CKD RCT)*

However, some of the interviewees were less certain and had a more practical approach on such matters. They believed that participation of different age groups should be decided by the medical professionals, perhaps based on the clinical appropriateness of individual research topics. Additionally, an interviewee also believed that such a cut-off might be unimportant as all patients would make their decisions regarding research participations based on their personal views.

*"The cut-off has got to be from the medical profession knowing is it any use to use somebody over the age of 75 or something whatever figure you do. We are growing older. I think... I mean, I don't know medically about anything so what I am just saying is off the top of my head." Interviewee #10 (attended STOP-CKD RCT screening)*

*"You're the doctors, not me. I mean, I wouldn't know whether….. I have no idea. I mean surely it is for the benefit of the public, so whatever age you want you deal with. I don't know. I mean I don't think it matters. If people don't want to do it, they won't." Interviewee #12 (declined to participate in STOP-CKD RCT)*

## 7.4 **Discussion**

Patients' willingness to participate in research studies is likely to be influenced not only by design of studies but also by their attitude towards research. While several factors and various barriers for research participation have already been extensively examined by both quantitative and qualitative studies to date (466, 473, 475-478), the set-up of the STOP-CKD RCT and the target population were unique. Therefore, its

failure to recruit deserved a thorough and more individualised analysis. The principal findings emerging from this qualitative study identified the motivators and barriers to research participation pertinent to the STOP-CKD RCT and highlighted several crucial issues specific to the recruiting of patients with CKD in primary care. Additionally, it also gathered suggestions for future research improvement and importantly, valuable opinions with regard to inviting the elderly population to participate in clinical trials.

Though prior research experience was common amongst the interviewees and the majority considered their past experience to be positive, most of the experience was limited to participation in observational studies. A survey study of 386 African Americans found that those who had previously participated in clinical trials had more positive views towards research compared to those without (485). Other quantitative surveys also demonstrated that people with prior research experience were potentially more willing to participate in future research (486, 487). Nevertheless, this interview study appeared to suggest otherwise. Many of those who declined to participate in the STOP-CKD RCT had in fact been participants in observational research studies. Hence, it seemed that factors other than the general positive attitudes towards research were far more influential in governing patients' decisions on their participation in interventional studies. In addition, the issue with the research team's delay in communicating incidental findings to patients' GPs noted within this theme also represented an important learning point for future studies.

In general, altruism (469, 478, 488-491) and self-interest (469, 489-494) are often cited to be central in determining their willingness to participate in any research

studies. Indeed, within the context of the STOP-CKD RCT, both were found to be the recurring factors stated by most of the interviewees during the interview. Their altruistic notion appeared to be based on the belief that research studies would advance medical knowledge in CKD, improve treatments, 'find a cure' and ultimately 'benefit others'. Conversely, their self-interest was governed by whether they perceived their participation would achieve personal gain by enhancing their knowledge of CKD, having additional health monitoring, improving their health status or resulting in personal loss as the consequences of trial medications' side effects and the additional demands of the trials on their daily lives. Intriguingly, apart from one of the interviewees who expressed her 'duty of altruism' as the sole reason, others often described these two factors collectively as the reasons for research participation. As altruism is supposed to be a selfless notion, one might therefore question the 'pureness' of such altruism cited by the interviewees. Overall, how significant was the role of self-interest, in relation to altruism, in driving such research participation? This question is perhaps best assessed in those who declined to participate in the STOP-CKD RCT.

Most of those who declined to participate in the STOP-CKD RCT acknowledged the importance of CKD research for the public interest. However, despite such understanding, their perceived personal loss or the failure to perceive any potential personal gain ultimately hindered their participation. This implied that safeguarding one's personal interest is most probably the single decisive factor in this process. It also supported the notion that altruism cited as the reason for research participation is 'conditional', requiring not only the absence of personal loss, but also the presence of perceived personal gain. This finding of the magnitude of the effect of self-interest on

research participation is in agreement with the previously published studies (471, 493). In a literature review of the ethics of RCTs, Edwards et al noted that self-interest was expressed more frequently than altruism as the reason for participating in trials, irrespective of whether the studies were based on concrete or hypothetical scenarios (493). Additionally, a qualitative interview study of patient decisions about recruitment to an epilepsy treatment trial also found that participants often applied 'weak altruism' while maintaining their self-interest (469). Similarly, McCann et al used 'conditional altruism' to describe the fact that though altruistic tendencies encouraged trial participation, it was on the condition that there were perceived personal benefits and the absence of overriding concerns in a qualitative study of people invited to participate in an RCT comparing medical and surgical interventions for gastro-oesophageal reflux disease (468). Hunter et al went one step further and concluded that the opportunity to benefit directly was the primary, if not, the only motive of research participation (495).

Such motive of personal gain warrants exploration. Given clinical equipoise being the fundamental principal of any RCT and that there are in fact genuine clinical uncertainties related to the trial intervention, why did some interviewees perceive potential significant personal gain from their research participation? Was there any 'therapeutic misconception' (469, 496)? Reassuringly, apart from one interviewee (interviewee #6) who might have slightly over-played the benefits of the trial intervention, most did not appear to have therapeutic misconceptions with regards to the trial intervention of the STOP-CKD RCT. In fact, an overwhelming majority agreed to take part in the STOP-CKD RCT in order to improve their personal knowledge regarding the condition or to receive additional medical attention and

monitoring. It is conceivable that being a silent and less known condition with considerably low illness awareness meant that these putative, non-specific trial effects become highly-valued benefits. Additionally, as patients have been shown to perceive CKD as a severe condition (detailed in Chapter 6), the opportunity to improve their understanding of such illness by taking part in research might, therefore, represent a significant appeal to their self-interest.

Of particular importance, such perceived gain also appeared to be heavily influenced by the perceived relevance of CKD to their health. Recently, Frew et al developed the Clinical Research Involvement Scales and demonstrated that the instrument was reliable for assessing community attitudes towards clinical trials participation (497). Factors included in the scales consist of behavioural belief, outcome evaluation, normative belief, motivation to comply, attitudes, subjective norms, organization involvement and personal relevance. Amongst which, 'personal relevance' was noted to have the strongest reliance (497). Indeed, Canvin et al underlined the fact that 'in agreeing to participate in a clinical trial, patients should first accept the clinical definitions of disease and the need for treatment, then be willing to entertain the possibility of clinical equipoise about which treatment to offer, and the need for evidence to resolve it…' (469). The health belief model, which was initially developed to understand the 'widespread failure of people to accept disease prevention or screening tests for the early detection of asymptomatic disease', (498) also appeared to be applicable to the understanding of patients' decision-making in CKD research participation. In the context of early to moderate CKD, where belief in the diagnosis is often hindered by low illness awareness as well as the lack of physical

symptoms, the health belief model of CKD interestingly appears to be more akin to that of the preventative health behaviour than the sick role behaviour.

The striking disparity amongst the interviewees in their acceptance or rejection of a diagnostic label of an asymptomatic long-term condition, and therefore resulting in either the acknowledgment of or disagreement with the diagnostic significance and requirement of intervention was an interesting finding of this study. Whilst unawareness of a diagnosis of CKD motivated some of the interviewees to participate in the STOP-CKD RCT in order to glean further information to fill in their knowledge gap regarding their health, for many others, it represented a barrier as they unequivocally rejected the diagnosis and failed to see the relevance of the study or the benefit of being involved. A previous quantitative study reported 'feeling healthy' together with 'no interest' and presence of 'current medical treatment' as the main reasons for non-participation in a lifestyle interventional study in a group of men with high CV risk (499). Likewise, a qualitative interview study found that the lack of perceived need was one of the most cited reasons for not participating in a telephone care management program (480). It seemed that as many of this CKD population 'feel well', some of the interviewees did not only question the diagnosis of CKD, but also the need for intervention. The issues of low illness awareness and asymptomatic nature pertinent to early-stage CKD therefore affected not only their perception of susceptibility, but also influenced the perceived severity or consequences of CKD. In addition, such rejection of the diagnosis of CKD was also likely to be closely linked with their misconception of the disease terminology, often dominated by fear, as highlighted in Chapter 6. These issues therefore represent crucial barriers pertinent to

the recruitment of early CKD patients into interventional research studies especially in primary care setting.

A survey in Germany found that even though almost 90% of the public judged clinical trials as important, only a quarter were willing to take part in the trials (486). Evidently, despite a generally positive attitude towards research, there are multiple barriers to research recruitment and such issues have been extensively investigated in various populations (478, 494, 500, 501). A systematic review by Ross et al summarised from the patients' perspective reported that the additional trials procedures and appointments, travel problems and costs, preferences for no treatment or a particular treatment, concerns about information and consent as well as the uncertainty associated with the treatment or trials were the main participation barriers in RCTs (478). Indeed, this interview study reaffirmed those findings as the impact of trials on patients' daily lives, the increased medication burden and the invasiveness of trial procedures were identified as some of the common barriers for participation. However, 'fear or uncertainty' was the consistent, recurring factor highlighted by the majority of the interviewees as the main barrier to research participation. This is in agreement with the finding of a survey of 100 cancer outpatients whereby awareness, fear and myths about clinical trials participation were noted to be the key issues (502). According to the data which emerged from this interview study, this notion of 'fear' appeared to be driven predominantly by their sense of uncertainty with regards to various aspects of trials, including but not limited to the possibilities of incidental findings during the screening process, treatment assignment, treatment effects, end-of-trial arrangement and the perception of being the subject of an experiment. While some of these fears might be alleviated by the provision of further information or

judicious reassurance by the researchers, it seemed that the fear was also governed by the individual's ability to accept such uncertainty which was unavoidably the nature of most RCTs. Indeed, a previous qualitative study demonstrated that while the concept of clinical equipoise was understood by the majority of the patients, those who found it acceptable were more likely to consent to the randomisation process and vice versa (503).

While John Harris argued that everyone should have a positive moral obligation to not only pursue research, but also participate in it as a mandatory contribution to the public good (504), it was clear that some of the interviewees did not agree with his notion. In the face of uncertainty, many often prioritised their personal interest over the potential public good. Some of the willing participants of the STOP-CKD RCT suggested that there might be a 'letting somebody else do it' mentality amongst those who declined to participate, akin to the so-called 'free riding' behaviour. As safeguarding of self-interest was the predominant factor, it was plausible that as the risks and uncertainty associated with interventional studies were perceived to be high, some logically chose not to participate in the study in order to minimize their individual 'costs' relative to the potential benefits they might receive from others' collective effort. Interestingly, based on economics models, Sandler et al published their mathematical deductions concluding that there was greater tendency for 'free riding' behaviour with increased uncertainty (505).

With regards to the impact of study characteristics on willingness to participate, a Swiss quantitative survey study found that destruction of blood samples at the end of a trial, use of placebo controls and a randomisation process were associated with

reduced likelihood of participation whilst new drugs without side effects, no additional visits and provision of balanced information encouraged participation (506). Neither the source of funding or financial reward influenced the decision in the same survey (506). During this interview study, it appeared that participants' trust in researchers was central to their acceptance of the trial intervention. The rejection of one of the interviewees to be involved in the interventional study might not only reflect her aversion towards taking additional medication, but also hint at her slight mistrust of the research team in contrast to her faith in her GP. With regard to the trial setting, the majority preferred the convenience of a primary care setting compared to travelling to secondary care location. Although it appeared that most of the interviewees did not seem to mind the duration or frequency of research visits, this might be biased by the fact that many of them were retirees. In contrast to the findings of a survey by Agoritsas et al (506), there seemed to be diverse views on research funding sources amongst the interviewees in this study. Some interviewees expressed no bias against or preference for research from different funding sources with the understanding that there is limited research budget from non-industry sources. Nevertheless, many others were either hesitant towards, or completely opposed, research funded by pharmaceutical companies as they were concerned about the conflict of interest. With the CV trials funded by for-profit organisations found to be more likely to favour newer treatments compared to their counterparts (507), it is perhaps justifiable for the interviewees to have such wariness towards industry-sponsored research. Djulbegovic et al concluded that such bias was attributed to their violations of the principle of equipoise in regards to the study design and results reporting (508). However, with 92% of the new chemical entities approved by the US Food and Drug Administration (FDA) in the 80's having been developed by

pharmaceutical companies (509), it is perhaps unreasonable to disregard industrial-sponsored research as a whole. Furthermore, as the pharmaceutical industry's annual worldwide budget for drug development exceeds $6 billion (510), the solution to such bias and issues related to industry sponsored research might not be as simple as demanding that governments increase healthcare research budgets.

In addition to detailing the key factors influencing research participation amongst patients with early to moderate CKD, this study also reported on their views on inclusion of the elderly in clinical trials. It is a well-known fact that GFR declines with advancing age (511). Nevertheless, the reasons for such decline as a normal physiological process or a pathological condition remain a heavily debated topic (511, 512). The proposal by one of the general practices to exclude elderly patients from the STOP-CKD RCT invitation during the set-up of the study indicated not only a certain scepticism about the definition of CKD in the elderly population amongst some of the GPs, but also implied that there are preconception based on patients' age regarding their fitness and willingness to take part in research. Data regarding the influence of age on willingness to research participation has been conflicting in the literature to date (486, 487, 494, 513). A systematic review found that in general, elderly patients did not regard age as the main reason for declining to take part (514). In fact, a survey of elderly oncology patients demonstrated that most were willing to consider research participation but few were informed of the availability of the clinical trials indicating that the barrier to the research recruitment of elderly patients might be physician or research-related (515). The findings from this interview study were in agreement with those of Townsley's (515). The majority of the interviewees believed that the elderly patients should be invited to participate in research on the grounds that they deserved

a voice and importantly, warranted a sufficient representation in the research population. In the context of CKD whereby the elderly comprise a substantial proportion of the population, it is clearly all the more important to ensure that the findings of CKD research are generalisable and applicable to this subgroup of patients. Though selection bias cannot be excluded, none of the interviewees objected to the inclusion of elderly patients in clinical trials. While some thought that such issues should be the decision of healthcare professionals, many were enthusiastic and passionate about elderly population being included and felt that this group of patients were probably more willing to engage in research studies.

Several suggestions were also made regarding the STOP-CKD RCT trial process, which may serve as learning points for further studies. Wording of the invitation letter, sequence of screening procedures, discomfort during blood pressure measurement, and the quantity of blood taken were some of the concerns mentioned. Furthermore, a few of the interviewees also suggested a more personal recruitment approach, advertising the research, incorporating enrolled participants' comments in future research invitation letters or extending recruitment hours to aid the recruitment rate. Further research in identifying the effectiveness of such recruitment methods in CKD research is clearly warranted.

### 7.4.1 Limitations

This interview study has several limitations. As only the latest recorded eGFRs was used to short-list eligible patients for the STOP-CKD research invitation, it is plausible that not all interviewees have a confirmed diagnosis of CKD. In addition, there was a preponderance of patients with older age and white ethnicity. As the

majority of the patients were above the age of 65 years and not in work or had retired, this might influence their views regarding research participation especially in regards to study duration and frequency of visits. As advancing age is known to be associated with increasing disease prevalence and medication use (516), their views on participation in clinical trials involving pharmacological intervention could also potentially vary from those of the younger age. Furthermore, due to the absence of non-whites, the study was unable to explore the issue of potential ethnic differences in the perception of both CKD diagnosis and research participation. Although significant efforts were put into maximizing the representativeness of interviewees, this study was still limited by patients' self-selection that could lead to bias in the findings. It is possible that patients who were willing to taking part in this interview study, despite having declined to participate in the STOP-CKD RCT, had dissimilar views on CKD or research participation compared with those who declined participation in both the RCT and the interview study. In addition, while the interviewer aimed to maintain a neutral attitude during the interview study, her role as a nephrology registrar in a tertiary hospital as well as an active clinical researcher who was involved in the recruitment of both the STOP-CKD RCT and the interview study might have resulted in potential biases. As the interview study focused mainly on CKD in primary care in the UK, the findings might therefore not be necessary applicable to other illnesses in different settings and in different countries.

### 7.4.2 Conclusions

Despite these limitations, this study has identified 'perceived relevance of the research topic to personal health' as a significant prerequisite for patients' participation in CKD research in the primary care. Complementary to the findings of

Chapter 6, patients' perception of the term CKD was found to be influential in governing patients' decisions on research participation via their perception of susceptibility and severity of the said condition. Furthermore, this study also reaffirmed the importance of self-interest, in relation to altruism, as the primary motivator for research participation. Amongst all, improving personal knowledge of CKD through research participation appeared to be a highly valued benefit amongst this group of patients. While 'cues to action' often appear to be the foci of most recruitment strategies, it seems unlikely that such cues will result in research participation in the absence of 'perceived susceptibility', 'perceived severity' and 'personal gain'. Hence, further CKD research recruitment strategies should aim not only at 'cues to action', but also consider methods to overcome the much wider issues of low illness awareness and knowledge as well as misconception of the term CKD amongst the CKD population, all of which ultimately impact on patients' participation in CKD research, especially in primary care.

# CHAPTER 8 SUMMARY AND CONCLUSIONS

Chronic kidney disease represents the 19th leading cause of global loss of life (1). It is a growing and important public health issue, which affects up to 14% of the population of the developed world (2-5). While patients with CKD undoubtedly have heightened risk of progressing to ESRD, their competing risk of death was far greater (6). This significant increase in mortality amongst the CKD population appeared to be heavily driven by their excessive CV burden (41).

However, this increased CV burden observed in patients with CKD is not fully explained by traditional CV risk factors as the Framingham risk score which is based upon age, gender, DM, systolic BP, smoking status and cholesterol profiles has been shown to significantly under-estimate CV events in patients with CKD at 5 and 10 years (60). While patients with CKD are at high risk of developing vasculo-occlusive, atheromatous disease including myocardial infarction or peripheral vascular disease, they are also at much higher risk of developing non-vasculo-occlusive, arteriosclerotic disease leading to heart failure and arrhythmias. Increased arterial stiffness is believed to be the key, early mechanistic pathway leading to such CV abnormalities in the CKD population (58) which is evident even in the early stages (65, 66) despite satisfactory BP control (67). Nevertheless, the reasons for this increased arterial stiffness found in patients with CKD are poorly understood (58).

Crucially, there is a significantly lack of RCT data (141) and an over-reliance on *post-hoc* or subgroup analyses of studies in the general population (142) in guiding the management of this heightened CV risk in the CKD population. Indeed, a recent

authoritative and comprehensive systematic review struggled to find large, high quality RCTs from which to make strong recommendations on screening, monitoring and treatment of early stage CKD (166). Additionally, while majority of the CKD studies were conducted in the secondary care settings, patients with stage 3 CKD in the U.K. are in fact mostly managed in the primary care setting (395, 396) and are often older with less well-defined renal phenotypes than the patients included in the hospital-based study.

The works presented in this thesis therefore attempt to address some of the issues highlighted above.

*1. Could treatment with xanthine oxidase inhibitor be an intervention to be tested in a future feasibility RCT aims at lowering arterial stiffness in CKD? (Chapter 2)*

Hyperuricaemia is highly prevalent among CKD population (194). Asymptomatic hyperuricaemia is associated with increased CV and all-cause mortality in both the general population (183-188) and in patients with CKD (194-196, 303-305). To date, a small number of studies exploring the use of the xanthine oxidase inhibitors (i.e.: allopurinol and febuxostat) in patients with CKD have demonstrated encouraging results in improving inflammatory markers, endothelial function, LVH, reduced hospitalisations, and lowering risk of CV events (198-201).

Using the data from a prospective, observational cohort study of CKD patients at high risk of renal disease progression, the study found an independent association between the use of allopurinol and lower arterial stiffness. Interestingly, there was no

direct association between serum uric acid levels and arterial stiffness, suggesting that the beneficial effect of allopurinol on arterial stiffness is likely to be attributable to its anti-oxidant property rather than its uric acid lowering effect. Although the study was limited by its observational nature and therefore does not prove causation, the finding nevertheless adds to the accumulating evidence of the favourable effect of allopurinol on CV outcomes (200, 213, 517) and indicates one mechanism by which this may occur. It also provides further justification for a definitive RCT to fully examine the therapeutic potential of xanthine oxidase inhibitor in CKD. Perhaps most importantly, this study provides vital information to inform any future RCT by giving some idea of the potential effect size expected and thus the number of patients required to adequately power a study with arterial stiffness as the outcome measure.

*Future Directions*

Although there is an accumulating body of evidence indicating the beneficial effects of xanthine oxidase inhibitors on various CV surrogate markers, CV risk and CKD progression by small published studies (198-201), a large, multi-centre, randomised, hard-end points study would be required before allopurinol is recommended as a CV risk reducing intervention in patients with CKD. Allopurinol hypersensitivity syndrome is an infrequent but life-threatening adverse effect of allopurinol (518). Studies examining the safety of allopurinol use amongst patients with CKD have so far reported inconsistent findings (519). It is therefore crucial for further research to establish the safe, dosing profile of xanthine oxidase inhibitors for patients with different stages of CKD, especially if the indication for such therapy were to be broadened beyond the treatment of gout in the future. As such, preliminary feasibility and safety studies are currently being planned (520).

*2. Is there enough evidence to justify the routine use of MRAs to lower CV risk associated with CKD? (Chapter 3)*

To date, the renal and CV benefits of treatment with ACEi or ARB have been demonstrated in multiple large trials (347). They represent the principal therapeutic interventions for improving hypertension, proteinuria and CV risk in patients with CKD (228-230). However, despite initial reduction, plasma aldosterone levels have been found to return to pre-treatment levels in subgroups of patients after prolonged exposure to ACEi or ARB, a phenomenon termed 'aldosterone breakthrough' (234). Aldosterone is implicated in numerous deleterious CV effects (218-221, 227) and the use of MRAs which inhibit the action of aldosterone have been reported to attenuate some of those consequences (217) leading some commentators to label MRAs such as spironolactone as "renal aspirin" (349).

Given the potential theoretical benefits of aldosterone blockade on CV outcomes in CKD as well as the potential harm of hyperkalaemia and deterioration in renal function, a systematic review and meta-analysis was conducted to examine the CV effects of MRAs in patients with CKD. Overall, MRAs were found to effectively reduce both the SBP and DBP in patients with CKD, even amongst those who were already receiving ACEi and/or ARB. Nevertheless, these beneficial BP-lowering effects were counterbalanced by an associated increase of serum potassium and risk of hyperkalaemia. The meta-analysis did not demonstrate any significant change in serum creatinine or GFR with the use of MRAs. Although a few short-term studies reported beneficial effects of aldosterone blockade on several CV surrogate markers,

due to the limited quality and quantity of the evidence thus far, it remains unclear if MRAs improve long-term CV outcomes in addition to their BP-lowering effect (249, 357, 375, 376, 379). Encouragingly a recent open-label study of 309 haemodialysis patients reported statistically significant reduction in CV morbidity and mortality at three years in patients receiving daily spironolactone of 25mg (391). Though the findings of this systematic review and meta-analysis do not support the routine use of MRAs to lower CV risk in patients with CKD, it does provide further evidence to support further RCTs in CKD to establish the risk and benefits associated with such an intervention in patients with different stages of CKD.

*3. Does low-dose spironolactone safely lower arterial stiffness in patients with CKD stage 3 managed in primary care? What is the feasibility of conducting a large and appropriately powered future trial examining hard end-points in primary care? (Chapter 4 methodology, Chapter 5 results)*

In a previous double-blind, placebo-controlled RCT, low-dose spironolactone safely lowered arterial stiffness in patients with CKD stage 3 managed in secondary care (140). However, most patients with CKD are in fact managed in primary care (395, 396). Additionally, they are often older and are less likely to be proteinuric than patients included in hospital-based studies, factors that could theoretically be associated with less benefit and more harm from MRA treatment. Furthermore, monitoring of potassium and renal function may be significantly more difficult from primary care. Thus, it is not known whether low-dose spironolactone can be used safely to lower arterial stiffness in patients with stage 3 CKD managed in primary care or whether a future, larger trial examining hard-outcomes would indeed be

feasible. Hence, the STOP-CKD trial was designed as a pilot study to examine whether low dose spironolactone safely lowers arterial stiffness in patients with CKD stage 3 managed in primary care. It was also designed to examine potential barriers to recruiting a large and appropriately powered future trial examining hard end-points.

Despite attempting to invite and screen for research participants who were representative of the 'real-life' CKD population in primary care, the STOP-CKD pilot RCT was terminated early due to poor recruitment. Although the study failed to provide scientific evidence regarding the effectiveness or the safety of the use spironolactone on patients with stage 3 CKD in the primary care, several observations made from this study are nonetheless valuable in informing and facilitating future CKD studies: (1) the distinct characteristics of patients with stage 3 CKD recruited in primary care in comparison to those in the secondary care and (2) the barriers and recruitment issues pertinent in conducting RCT in CKD population in primary care setting.

In contrast to previous CKD studies, patients who were invited, screened and eventually randomised for the STOP-CKD RCT were older, with a mean age of 71 years. This was in keeping with the epidemiological finding of the NEOERICA study whereby 50% of patients with stage 3a and more than 80% of those with stage 3b CKD were older than 70 years (37). Additionally, the degree of CKD among this cohort of patients was also found to be modest with most having no or only a mild degree of albuminuria, an unclear cause of CKD and a surprisingly large proportion having low SBP which precluded a signification number of patients from participating in the STOP-CKD RCT. These unique characteristics of patients recruited to this

study are clinically important and challenge our preconceived knowledge on the appropriate intervention and management of the non-diabetic CKD population in primary care. With the majority of interventional studies in CKD patients thus far conducted from secondary and tertiary centres, there is undoubtedly a need to reconsider the study design and choices of intervention for future CKD studies in order to optimise the generalisability of future CKD research, especially in the early stages.

In the course of the STOP-CKD study, numerous barriers pertinent to the recruitment of the non-diabetic, stage 3 CKD population in primary care arose and resulted in the early termination of the study. The study highlighted the over-estimation of CKD prevalence in the literature, the difficulties faced in enrolling general practices as recruiting sites as well as the inefficiency of large mailshots as patient recruitment strategies for an interventional CKD study, all of which in return necessitated significant inflation of the number of the patients needed to be invited in order to recruit to the planned sample size. Although research-active practices appeared to have a positive influence on patients' reply to research invitation, it did not appear to translate to actual research recruitment. The experience and lessons learnt from this study clearly provide important information for all CKD researchers, especially those in the UK, to meticulously reflect on their future research aims, study design, choices of intervention and most importantly recruiting strategies.

*Future Directions*

Overall, the results of the systematic review detailed in Chapter 3 highlighted the need for high-quality, definitive research trials in evaluating the CV role of MRAs in

CKD. Nevertheless, the STOP-CKD study was terminated early to due to poor recruitment. The information gleaned from this study should help inform and assist other trials planned in this population to succeed. The finding of the STOP-CKD study that patients with CKD in the primary care are older, have more modest reduction of eGFR and less prevalence of albuminuria, in comparison to their counterparts in the secondary care setting, is in agreement with the previous study (521). However, research evidence with regard to the appropriate management of the CKD population in the primary care remains scarce. Additionally, the current clinical practice often derives from the research outcomes of those from the secondary care despite the distinct disparity between the groups. With a recent systematic review showing that intensive BP control reduces the risk of renal progression, but only amongst those with proteinuria (147), there is clearly a need for further research to better characterise the long-term outcomes as well as define the risk modifiers, specific to the CKD population managed in the primary care. Such research data will be invaluable not only in guiding the day-to-day management, setting the clinical guidelines as well as audit standards, but also directing future research questions and interventions.

Furthermore, hyperkalaemia is a well-established adverse effect associated with the use of MRAs. In particular for the CKD population already receiving ACEi or ARB, issues with hyperkalaemia may potentially affect the risk:benefit ratio of MRA therapy and limit its clinical applicability. Two new oral agents, Patiromer (522) and Zirconium Cyclosilicate (523), have so far shown promising short-term outcomes in the treatment of moderate hyperkalaemia, including patients with CKD. Nonetheless,

their durability, side effect profiles and potential to permit wider, long-term usage of MRA will required further investigations.

Effective and efficient recruitment strategies are indispensable for the success of any research study. The STOP-CKD study demonstrated that large mailshot of interventional research invitation to CKD population is not a cost-effective method of recruitment and is often liable to patients' self-selection bias. There is clearly room for innovative recruitment strategies which require further exploration.

A large prospective, randomised, open blinded end-point trial (BARACK D study) aiming to determine the effect of MRA on mortality and CV outcomes in patients with stage 3b CKD in primary care is currently ongoing (524). Encompassing stage 3b CKD population with a minimal SBP of 100 mmHg, and including those with Type 2 DM; the participants' criteria of BARACK D study varies somewhat from that of the STOP-CKD. To date, it has recruited 16% of its target sample of 2,910 participants, however, the recruitment is significantly falling behind schedule and rescue proposals have recently been submitted to its funding body (personal communication, supervisor). Its findings, assuming the trial successfully recruits, are eagerly anticipated.

*4. What are patients' illness perceptions of early or moderate CKD in primary care and what are the barriers to patients' participation in CKD research study? (Chapter 6 & 7)*

Although there is an increasing number of a quantitative research study exploring the effects of various pharmacological interventions in improving CKD outcomes, issues regarding patients' illness experience and disease perceptions on CKD, especially in the early or moderate stage remain under-researched. In addition, despite the potential of clinical research to advance medical treatments, poor recruitment, as faced by the STOP-CKD RCT, is regrettably a chronic and ubiquitous issue. Understanding patients' illness perception of CKD and exploring their attitudes towards research participation are therefore two imperative steps in formulating strategies to enhance delivery of healthcare in CKD and improve future CKD research recruitment. Characterised by its ability to produce rich, comprehensive and in-depth data, qualitative research is therefore an ideal method to address such complex or unquantifiable social and healthcare research questions (404).

In agreement with the literature (438, 440, 441), the qualitative interview study embedded within the STOP-CKD trial found that the majority were often unaware of their CKD diagnosis. Furthermore, the study also reported issues with uncertainty of illness identity and negative misconceptions of the term CKD amongst the interviewed patients. It highlighted the importance of the disclosure of CKD diagnosis by healthcare professionals in order to address patients' illness perceptions, avoid misconception and minimise unnecessary stress amongst the patients.

With regard to CKD research participation, the qualitative study reaffirmed the importance of self-interest, in relation to altruism, as the primary motivator. Importantly, 'perceived relevance of the research topic to personal health' was identified as a crucial prerequisite for patients' participation in CKD research in the

primary care. Such perception was found to be closely governed by patients' awareness of CKD diagnosis as well as their views on the term CKD. Further CKD research recruitment strategies should therefore consider methods to overcome the much wider issues of low illness awareness, uncertainty of illness identity and misconception of the illness terminology amongst the CKD population, all of which represent major barriers to CKD research recruitment in primary care.

*Future Directions*

The findings from the qualitative study suggest that there is a need to improve public awareness and knowledge of CKD, encourage healthcare professionals in disclosing the CKD diagnosis and ensure shared decision making. Illness identity and CKD terminology represent two of the key areas which warrant attentive clarification by the healthcare providers during CKD diagnosis disclosure to the patients in the future.

As low awareness of CKD diagnosis amongst the patients appears to be one of the key reasons for poor recruitment, future research into the other barriers to disclosure of CKD diagnosis by the healthcare professionals will be useful to mitigating the issue. Importantly, improving our understanding of patients' experience of such disclosure and the impact on their self-management of health as well as willingness to research participation should also be the focus of future CKD research in the primary care.

While the chronic issue of poor recruitment and uncertainty of generalisability continue to challenge the running of most clinical trials, the future perhaps lies in

expanding patients' involvement not only in their healthcare, but also their engagement in research world.

# LIST OF PUBLICATIONS

## Publications Arising from the Thesis

**Ng KP**, Gill PS, Heer G, Townend JN, Freemantle N,Greenfield S, McManus RJ, Ferro CJ. Results and lessons from the Spironolactone TO Prevent cardiovascular events in early-stage Chronic Kidney Disease (STOP-CKD) randomised controlled trial. *BMJ Open.* 2016;6:e010519

**Ng KP**, Arnold J, Sharif A, Gill P, Townend JN, Ferro CJ. Cardiovascular actions of mineralocorticoid receptor antagonists in patients with chronic kidney disease: A systematic review and meta-analysis of randomized trials. *J Renin Angiotensin Aldosterone Syst.* Mar 17 2015.

**Ng KP**, Stringer SJ, Jesky MD, et al. Allopurinol is an independent determinant of improved arterial stiffness in chronic kidney disease: a cross-sectional study. *PLoS One.* 2014;9(3):e91961.

**Ng KP**, Jain P, Heer G, et al. Spironolactone to prevent cardiovascular events in early-stage chronic kidney disease (STOP-CKD): study protocol for a randomized controlled pilot trial. *Trials.* 2014;15:158.

## Other Publications

**Ng KP**, Moody WE, Chue CD, et al. Central pulse pressure in patients with chronic kidney disease and in renal transplant recipients. *J Hum Hypertens.* Mar 2014;28(3):180-185.

**Ng KP**, Edwards NC, Lip GY, Townend JN, Ferro CJ. Atrial fibrillation in CKD: balancing the risks and benefits of anticoagulation. *Am J Kidney Dis.* Sep 2013;62(3):615-632.

Stringer S, Sharma P, Dutton M, Jesky M, **Ng K**, Kaur O, Chapple I, Dietrich T, Ferro C, Cockwell P. The natural history of, and risk factors for, progressive Chronic Kidney Disease (CKD): the Renal Impairment in Secondary care (RIISC) study; rationale and protocol. *BMC Nephrol.* Apr 25 2013;14(1):95.

**Ng KP**, Townend JN, Ferro CJ. Randomised-controlled trials in chronic kidney disease--a call to arms! *Int J Clin Pract.* Oct 2012;66(10):913-915.

# APPENDICES

Appendix 3-1: Data collection form for systematic review and meta-analysis of CV effects of mineralocorticoid receptor blockers in patients with chronic kidney disease.

First author/study title: _____

| **Method** | |
|---|---|
| Country | |
| Setting (i.e.: multicentre) | |
| Time Frame | |
| Randomisation method | |
| Blinding | Participants:<br>Investigators:<br>Outcome assessors:<br>Data assessors: |
| Intention-to-treat: | Yes / No |
| Duration of follow-up | |
| Lost to follow-up | Treatment group:<br>Control group: |
| **Participants** | |
| Inclusion criteria | |
| Exclusion criteria | |
| Treatment group | Age:<br>Male : Female:<br>Others: |
| Control/comparator group | Age:<br>Male : Female: |

| | | |
|---|---|---|
| | Others: | |
| **Interventions** | | |
| Treatment group | | |
| Control/comparator group | | |
| Duration of intervention | | |
| Co-interventions | | |
| | | |
| | Treatment group | Control group |
| Total randomised | | |
| Excluded* | | |
| Observed | | |
| Lost to f/u* | | |
| Reasons for loss/exclusion: | | |
| **Outcomes** | | |
| Outcomes | Methods of measurement/ Definitions | |
| | | |
| | | |
| | | |
| | | |
| | | |
| | | |
| | | |
| **Notes** | | |
| Request for further information:<br><br>Clarification of methods:<br><br>Clarification of results:<br><br>Funding source:<br><br>Others: | | |

Appendix 3-2: Risk of Bias Assessment Form

First author/study title: _____

| **Study design** | **Parallel/crossover** |
|---|---|
| Was the allocation sequence adequately generated? | Yes / No / Unclear<br>Comments: |
| Was allocation adequately concealed? | Yes / No / Unclear<br>Comments: |
| Was knowledge of the allocated interventions adequately prevented during the study? | Participants: Yes/ No/ Unclear<br><br>Investigator: Yes / No / Unclear<br><br>Outcomes assessors: Yes / No / Unclear<br><br>Data assessors : Yes / No / Unclear |
| Outcomes assessment and measurement | |
| Intention-to-treat analysis | |

Appendix 3-3: Risk of bias assessment of all included studies

| Study | Allocation sequence generation | Allocation concealment | Blinding of participants and personnel | Blinding of outcome | Incomplete outcome data | Selective reporting | Other bias |
|---|---|---|---|---|---|---|---|
| **Rossing et al, 2005 (372)** | Low | Unclear | Low | Unclear | Low | Low | Low |
| **Schjoedt et al, 2005 (374)** | Low | Unclear | Low | Unclear | Low | Low | Low |
| **Bianchi et al, 2006 (355)** | Low | Unclear | High | High | Low | Unclear | Low |
| **Chrysostomou et al, 2006(358)** | Low | Unclear | Low | Unclear | Low | Low | Low |
| **Epstein et al, 2006 (359)** | Unclear | Unclear | Low | Unclear | Unclear | Unclear | Unclear |
| **Matsumoto et al, 2006 (366)** | Unclear | Unclear | High | Unclear | Unclear | Low | Unclear |
| **Meiracker, et al, 2006 (368)** | Unclear | Low | Unclear | Unclear | Unclear | Low | Unclear |
| **Takebayashi et al, 2006 (377)** | Unclear | Unclear | Unclear | Unclear | Low | Unclear | Unclear |
| **Joffe et al, 2007 (364)** | Unclear | Unclear | Low | Unclear | Unclear | Unclear | Unclear |
| **Furumatsu et al, 2008 (361)** | Unclear | Unclear | High | High | Low | Low | Unclear |
| **Saklayen et al, 2008 (373)** | Unclear | Unclear | Low | Low | Low | Unclear | Unclear |
| **Tylicki et al, 2008 (378)** | Low | Unclear | High | High | Low | Low | Low |
| **Edwards et al, 2009, 2010, 2012 (140, 248, 249)** | Unclear | Unclear | Low | Unclear | Low | Low | Low |
| **Guney et al, 2009 (362)** | Unclear | Unclear | Unclear | Unclear | Unclear | Low | Unclear |
| **Mehdi et al, 2009 (367)** | Low | Unclear | Low | Unclear | High | Low | Low |
| **Morales et al, 2009 (369)** | Unclear | Low | Unclear | Unclear | Low | Low | Unclear |
| **Taheri et al, 2009 (375)** | Unclear | Low | Low | Unclear | Unclear | Unclear | Unclear |
| **Vukusich et al, 2010 (379)** | Unclear | Low | Unclear | Low | Low | Low | Unclear |
| **Abolghasmi et al, 2011 (354)** | Unclear | Unclear | Unclear | Unclear | Low | Low | Unclear |
| **Boesby et al, 2011 (356)** | Unclear | Low | High | High | Low | Unclear | Unclear |
| **Zheng et al, 2011 (380)** | Unclear | Unclear | Unclear | Unclear | Low | Unclear | Unclear |
| **Nielsen et al, 2012 (370)** | Low | Low | Low | Unclear | Unclear | Unclear | Unclear |
| **Taheri et al, 2012 (376)** | Unclear | Unclear | Unclear | Unclear | Low | Unclear | Unclear |
| **Boesby et al, 2013 (357)** | Unclear | High | High | High | Low | Low | Unclear |
| **Esteghamati et al, 2013 (360)** | Unclear | High | High | Unclear | Low | Low | Unclear |
| **Hase et al, 2013 (363)** | Unclear | High | High | Unclear | High | Unclear | Unclear |
| **Lizakowski et al, 2013 (365)** | Unclear | Low | Low | Unclear | Unclear | Unclear | Unclear |
| **Nielsen et al, 2013 (371)** | Unclear | Low | Low | Unclear | Unclear | Unclear | Unclear |
| **Ziaee et al, 2013 (381)** | Unclear | High | High | Unclear | High | High | High |

Appendix 4-1: STOP-CKD working instruction for general practice electronic records search



| STOP CKD SEARCH – EMIS LV | | |
|---|---|---|
| Author(s):<br>Gurdip Heer | Function:<br>Research Nurse | Signature: |
| Approved by:<br>Dr C Ferro | Function:<br>Chief Investigator | Signature: |
| Document code:<br>WI05 | Version Number:<br>1.1 | Supercedes:<br>1.0 |
| Issue date:<br>17.07.2013 | Implementation date:<br>17.07.2013 | Reason for change:<br>Protocol version updated<br>Updated exclusion criteria<br>Added ethnicity to reporting |
| Reviewers:<br>Gurdip Heer | Function:<br>Research Nurse | Next review date:<br>2 years from date of issue |

Amendments procedure
Any amendments to this document must only be made by author in consultation with the chief investigator. Temporary amendments must be typed on an amendment pro-forma and inserted at the appropriate point. Details of these amendments must be listed below.
Revision History

| Date | Brief Description of Changes | Name | Signature |
|---|---|---|---|
| | | | |

Interim Changes

| Date | Section(s) | Page(s) | Brief description of amendments | Signature |
|---|---|---|---|---|
| 17.07.2013 | | 2 | Protocol version updated | |
| 17.07.2013 | | 7 | Ethnicity added to reporting | |
| 17.07.2013 | | 8 | Exclusion criteria updated | |
| 17.07.2013 | | 9 | Codes for exclusion listed | |

Purpose
The purpose of this document is to ensure that the study search, procedures for generating mail merge and identifying and removing in eligible participants are standardised across all GP practices using EMIS LV.

Scope
The scope applies to all the STOP CKD study team, delegated person/s working on behalf of the study team who are assisting GP practices in the task of undertaking the study search in EMIS LV as well as delegated person/s requested to carry out the study search at collaborating GP practices.

In order to capture the true practice population with CKD stage 3, it is intentional that eGFR value between 30-59 ml/min is searched for rather than the read code for chronic kidney disease.

At no point should STOP CKD team take patient identifiable data from the practice.

Applicability
These procedures apply to STOP CKD study searches undertaken using EMIS LV.

The responsibility lies with the individual carrying out the search to check the read codes applied below are the same as those being used by the practice. If they any different, use those specific to the practice.

Entry Conditions:
A person following the information in this document must;
a) be competent in undertaking searches in EMIS WEB, OR
b) be under the supervision of a trained person.

Associated Documentation
CKD study Protocol version 4.0: 20th June 2013 Spironolactone to Prevent cardiovascular Events in Early Stage Chronic Kidney Disease: A Pilot Trial (STOP-CKD)

Responsibilities
It is the responsibility of the trial coordinator to ensure WI has been read.
It is the responsibility of the trial coordinator to maintain the training records.
It is the responsibility of the user to read and understand the document.

**STOP CKD –Study Search EMIS LV**

**EMIS LV search for potential participants for STOP-CKD Study**

Log in as usual on to the computer.

From the main menu select the following:-

**ST** Search and statistics
**B** Patient search
**A** Build and perform a new search
**A** Perform search on **current practice population**
**A** Add feature

To add a feature (**age range**):
Select **1** Age CR (carriage return)
Age range (>18years): Upper limit 110 years CR
Lower limit 18 years CR
**A** Shared
**A** Add another feature
Select 2 Classification CR
Select **Values and Investigations** CR
Type MDRD (GFR calculated abbreviation =MDRD) CR
AMDRD 30-59 (451E) CR
Enter Upper limit 59ml/min CR
Enter Lower limit 30ml/mi CR
B Date range (2 years prior to search date)
A Shared
A Add another feature

Select 2 Classification Code CR
Type 22J (O/E – Dead)
Select A to all CR
A No date range
B Exclude
A Add another feature

Select 2 Classification Code CR
Type 8HG (Died in hospital)
CR All of the following, consultant, hospital, referring doctor, reason urgency
A No date range
B Exclude
A Add another feature

Select 2 Classification Code CR
Type C10 (Diabetes)
A Diabetes
CR to select all type
A No date range
B Exclude
A Add another feature

Select 2 Classification Code CR

Type ZV57C (Palliative Care)
A CR
A No date range
B Exclude
A Add another feature

Select 2 Classification Code CR
Type 8BA2 (Terminal Care)
A CR
A No date range
B Exclude
A Add another feature

Select 2 Classification Code CR
Type G58 (Heart Failure)
A CR – select all CR
A No date range
B Exclude
A Add another feature

Select 2 Classification Code CR
Type G573 (Atrial Fibrillation/flutter)
A CR – select all CR
A No date range
B Exclude
A Add another feature

Select 2 Classification Code CR
Type 62 (Patient pregnant)
A CR - select all CR
B Add date range (one year prior to date of search)
B Exclude
A Add another feature
Select 2 Classification Code CR
Type C1541 (Addison's disease)
A No date range
B Exclude
A Add another feature

Select 7 Drugs (DU)
Search on all drugs? NO
Select Ingredient/brand – Type Warfarin CR
Select Warfarin Sodium (for all types of warfarin)
CR to select all types

You will be requested to complete a series of questions to include in the search for the drug – answer as follows:

All drugs – NO
Currently PX – Select All CR
Issued between – CR (no date range)
Frequency – CR
Continue - Y

B Exclude
A Add another feature

Select 7 Drugs (DU)
Search on all drugs? NO
B Select drug group
2 Cardiovascular system drugs (2.1) CR
2 Cardiac Glycosides (2.1)
CR Select all

You will be requested to complete a series of questions to include in the search for the drug – answer as follows:

Currently PX – Select All CR
Issued between – CR (no date range)
Frequency – CR
Continue - Y
B Exclude
A Add another feature

Select 7 Drugs (DU)
Search on all drugs? NO
B Select drug group
2 Cardiovascular system drugs (2.1) CR
3 Diuretics 2.2+ CR
4 Potassium Sparing Diuretics (2.2.3) CR
CR Select All

You will be requested to complete a series of questions to include in the search for the drug – answer as follows:

Currently PX – Select All CR
Issued between – CR (no date range)
Frequency – CR
Continue - Y
B Exclude
A Add another feature

Select 7 Drugs (DU)
Search on all drugs? NO
Select Ingredient/brand – Type Fludrocortisone Acetate CR
CR to select all types

You will be requested to complete a series of questions – answer as follows:

All drugs – NO
Currently PX – Select All CR
Issued between – CR (no date range)
Frequency – CR
Continue - Y
B Exclude
A Add another feature

Select 7 Drugs (DU)

Search on all drugs? NO
Select Ingredient/brand – Type Co-trimoxazole (must add hyphen)CR
CR to select all types

You will be requested to complete a series of questions - answer as follows:

All drugs – NO
Currently PX – Select All CR
Issued between – CR (no date range)
Frequency – CR
Continue - Y
B Exclude
A Add another feature

Select 7 Drugs (DU)
Search on all drugs? NO
B Select drug group
4 Central Nervous system drugs
3 Drugs used in psychoses and related disorders 4.2+
4 Lithium Salts (4.2.3)
CR Select All

You will be requested to complete a series of questions to include in the search for the drug – answer as follows:

Currently PX – Select All CR
Issued between – CR (no date range)
Frequency – CR
Continue - Y
B Exclude
A Add another feature

When the search has been completed press CR.

"Are features correct" will appear at the bottom of the screen.
If you are happy with the search press: YES.
Provide search title.
File: - One off Search CR (or wherever practice has specified)
"Do you want to run report" will appear on the bottom of the screen – press Y

If any changes need to be made to the search press E edit search (amend changes).
Save as above.

Searching the results of a search and generating report for mail shot

Return to **ST** on the main menu.
Select B patient searches
Select **S** Search Results
Find search One off search folder (or where ever the file has been saved)
Select search Select search (whatever title has been given). CR

Select **F** Report names and address plus aspects of patients' records
Select **A** Add new report.
This report generates the demographic details for the mailshot/contact numbers/ drug list and investigational values)
Select G Patient Number (adds patients Emis number)

Select A Add aspect
Select **A** Select the following from the registration details by pressing the spacebar.

- TITLE
- SURNAME
- FORENAME
- SEX
- DATE OF BIRTH
- HOUSE NAME/FLAT
- NO. and STREET
- VILLAGE
- TOWN
- POSTCODE
- ETHNICITY ( read code 9i)

**Note**: - in some practices *MAX of 11 options allowed*

Select F8 to save

Returning to Edit Collection menu
Select A add aspect
Select J Age
Select Age in years CR

Select A add aspect
Select E present medication
Select Current drugs
Select G Drug Group
Select 2 Cardiovascular systems drugs CR
Select 6 anti hypertensive 2.5+ CR
Select 6 drugs affecting Angiotensine system 2.5.5+ CR
Select 2 Angiotensine converting enzyme inhibitors 2.5.5.1CR
Include drug group select Yes CR

Select A Add aspect
Select E Present medication
Select Current drugs
Select G Drug Group
Select 2 Cardiovascular systems drugs CR
Select 6 Anti hypertensive 2.5+ CR
Select 6 Drugs affecting Angiotensine system 2.5.5+ CR

Select 3 Angiotension II receptor antagonists 2.5.5.2 CR
Include drug group select Yes

Select A add aspect CR
Select D Aspects of Clinical records
Select V Values and investigations CR
Type MDRD CR
Select A GFR calculated abbreviation -451E CR
Earliest Date CR
Latest Date (day of search) CR
Include latest –Y
Code description – N
Read Code – N
Date of entry – Y
Associated features – N
Text – N
Numerical Value – Y
Episode – N
CR

Data collection request for the search has now been completed.

Select P Print
Select 12 Export to Microsoft Excel CR

Indicate delimiter character (:) appears CR

Creating spool - file appears.

Save File – give it a title (STOP CKD demographics).

Select F8 to save report

Filtering results in Microsoft Excel to remove INELIGIBLE patients

Filtering the results to remove ineligible patients is an essential part of the search criteria.

Aim: From the generated search:

- Patients that are on both ARB and ACE need to be removed
- Patients with ethnic grouping: Black; Black British: Caribbean: Other Black background; Black African need to have their efgr modified by 1.2%
- Patients with latest eGFR result <30 or >59 need to be removed.

Removing patients that are on both an ACE and ARB
Method:

1. Copy the original search to new workbook. Name the workbook as exclusion criteria.
2. Highlight all the data
3. Using the sort icon from the tool bar
   Sort by: select column with ACE ascending order
   Add a level. Sort by: ARB. Select Ok to order the data.
4. Highlight any patient that is on **both an ACE and ARB** by looking at the data order, **these are to be removed from the potential list of participants for the study.**

Modifying the black ethnicity eqfr
Method:

1. In the same workbook highlight all the data

2. Using the sort icon from the tool bar
   Sort by ethnicity
3. Highlight all the black ethnic groups these include Black; Black British: Caribbean: Other Black background; Black African
4. Insert a column next to the reported egfr and label as modified Egfr
5. Work your way from the top of the page, looking at all the highlighted black ethnic participants egfr and multiply this by 1.2
   e.g egfr 52 ( 52x1.2=62.4) modified egfr would be 62
   if the number after the decimal point is equal or more than 5 then round up to the next whole number

**NB: Mixed black ethnicities are not to have their egfr modified**

Removing patients with an eGFR that is <30 or >59
Method:

1. In the same work book highlight all the data
2. Using the sort icon from the tool bar
   Sort by: selecting column with GFR value ascending order.
5. Highlight any patient on the list with values either <30 or >59 by looking at the ordered GFR column. **These are to be removed from the potential list of participants for the study.**

Copy the ineligible work book into a new workbook – remove all the highlighted patients that have an egfr <30 or >59 and/or those that are on an ACE and ARB.
Label the work book eg; "GP list"

The Search for potential eligible STOP CKD participants is complete.
Add a 2 columns at the end of the headers and label column 1 as reasons for exclusion by GP and label column 2 as codes for exclusion criteria.

The search is to be saved on the "Shared Drive" at the practice, give the file a name. The search is to be locked to avoid changes to results.

Locking the file: select tools: PROTECTION, select OPTIONS, select SECURITY,
Select READ ONLY availability
Add password (use standard password STOPCKD)
Confirm password
Inform study team of added password.

Print the potential list of participants for GP review. Apply a header and page number to the list and attach GP authorisation check list to the search.

To avoid any embarrassment to the practice or to the research team due to patient registration status/health changes request that the list is checked and ready for mail shot within 7 days (includes weekends). A little flexibility can be negotiated at the discretion of the practice manager and study co-ordinator.

Codes for exclusions

| Reason | Code |
|---|---|
| No longer registered with the practice | 4 |
| EGFR Normal | 5 |
| No reason provided for exclusion | 6 |
| Social problem– recent bereavement / does not speak English etc | 7 |

Appendix 4-2: STOP-CKD Patient research invitation letter

[GP Name, Address and Contact Number]

[Date as postmark]

Dear [Title and surname]

**Invitation to Participate in Research Study:**
STOP-CKD: Spironolactone to Prevent Cardiovascular Events in Early Stage Chronic Kidney Disease: A Pilot Trial

We are working with the Primary Care Clinical Research and Trials Unit at the University of Birmingham on a study that aims to look into the possible benefits of the use of a 'water-tablet', called Spironolactone in patients with early stage chronic kidney disease. We are writing to people from the practice to ask for their help and you have been selected as you have had a blood test in the past indicating you may have a lowered kidney function.

We would be very grateful if you would read the attached information sheet about the study and think about whether you would like to take part. Please indicate on the response slip whether or not you are interested in participating in the main study and/or the interview study. A FREEPOST envelope is enclosed for you to return your response directly to the research team at the University.

**If you have any questions about the study then you can contact the research team directly on**
**0800 923 0329.**

**Thank you for your time.**

Yours sincerely,

[Signature]

[Name]

[Practice Lead GP]

Appendix 4-3: STOP-CKD Patient Information Sheet

UNIVERSITY OF BIRMINGHAM

**STOP-CKD**

**Spironolactone to Prevent Cardiovascular Events in Early Stage Chronic Kidney Disease: A Pilot Trial Version 2.2 20/06/2013**

## Patient Information Sheet

We would like to invite you to take part in a research study. Before you decide, we would like 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. Talk to others about the study 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.

**Part 1**

**What is the purpose of the study?**

**About 1 in 10 people have mild chronic kidney disease (CKD)** most commonly because kidney function declines with age. Patients with kidney disease are at increased risk of hardening of the blood vessels, which can lead to heart disease and stroke. We are investigating a medication called Spironolactone which has been used to treat patients with high blood pressure, heart disease or liver disease for a long time. In patients with mild kidney disease in our specialist hospital kidney clinic, **Spironolactone** seems to improve heart function and reduces hardening of the blood vessels. We want to find out if Spironolactone has similar effects on patients with early kidney disease treated in the community.

**Do I have to take part?**

It is up to you to decide if you wish to join the study. If you agree to take part, we will then ask you to sign a consent form. You are free to withdraw at any time, without giving a reason. Your medical care will be unaffected whether or not you take part.

**Why have I been invited?**

You have been invited to take part in this research study because you have had a previous blood test at at your GP surgery that shows you may potentially have reduced kidney function.

**Who else is taking part?**

We are inviting people like you, from different GP surgeries in Birmingham to take part. We need to identify a total of 240 patients with early kidney disease to participate in this research study.

**What will happen to me if I take part?**

Participation in this study is **voluntary**. If you decide that you would like to take part in this study, you will be asked to attend a clinic at your own GP surgery run by the research team.

A member of the team will explain the study to you and answer any questions you might have. They will ask you some questions about your general health and any medication you may be taking. You will then be asked to sign a consent form. You should only do this if you are happy that you understand the project and want to take part. A urine sample and 30ml blood sample (less than 3 tablespoons) will be taken to confirm if you have reduced kidney function by a kidney specialist and if you are eligible to take part in this study.

If you are eligible, you will then be contacted by the research team and invited back to another clinic, also at your surgery. A member of the team will discuss the study with you again and check that there have been no changes to your health or medication. We will check your blood pressure, measure your weight, height, waist, hip and thigh circumference and measure the stiffness of your blood vessels. You will be asked to complete a questionnaire. A computer will then decide at random (like tossing a coin) which type of treatment you will have. Half of the people taking part will be prescribed the medication and the other half will be prescribed a placebo capsule (A placebo capsule looks similar to the active medication but contains no active drug). You will be prescribed the medication the computer chooses for you using a prescription that can be collected from one of our designated pharmacies. This medication needs to be taken daily for 10 months.

Over the course of the study, you will be seen by the research team at regular intervals (2, 4, 8, 16, 28 weeks) at your own surgery. They will again take your blood pressure measurements, repeat blood samples tests and completion of a Quality of Life questionnaire. At 40 weeks, we will repeat the measurement of your blood vessels' stiffness and collect blood and urine samples. You will be informed to stop the trial medication after the 40 week visit. At the end of the study (6 weeks after the trial medication is stopped), we will asked you to attend a final clinic to have a repeat blood and urine test, as well as repeat measurement of blood vessels' stiffness. So in total, you will be seen at your surgery 8 times.

**What will I have to do?**

You will need to take the study medicine regularly during the course of the study (40 weeks) and attend all the study visits. We will ask you to report any missed tablets during the study period. You should also continue taking all of your normal tablets. We will review your medication before you start the study to make sure the study medication does not interfere with your usual tablets.

We will ask you to tell us if your GP starts you on any new medicines during the study. If your Potassium level is found to be high on the blood test during the study period, we might ask you to restrict certain foods in your diet to avoid foods high in potassium and provide you with an information sheet.

**What happens at the end of the research study?**

Once you have completed all of your tests at the final visit, the trial medication (Spironolactone or placebo) will be stopped. The results will be studied and analysed. Your usual medical care will continue as before once the study is completed. All specimens collected during the study will be stored for 5 years after the completion of this study. If you would like to know the results we will send you a summary.

**Will I get paid for taking part?**

We are unable to pay you for participating but we will reimburse your travel expenses to and from your GP surgery or Queen Elizabeth Hospital Birmingham.

**What are the alternatives for treatment?**

There are currently no other medicines licensed for reducing stiffness of the blood vessels in patients with early kidney disease.

**What are the possible risks of taking part?**

With the exception of the blood tests, study procedures should not cause any pain or discomfort. There are small risks of increased levels of salts in the blood, reduced kidney function or low blood pressure with the use of Spironolactone, requiring the withdrawal of the medication. However, the dose of the trial medication is relatively low and you will be closely monitored by kidney specialists during the study to ensure that those risks are minimised.

Spironolactone should be avoided during pregnancy. If you are a woman of child-bearing age, we would ask you for permission to perform a pregnancy test prior to starting the trial medication and to agree not to become pregnant whilst taking it. If you do become pregnant during the course of the study, you must stop taking the trial medication immediately and inform our research team so an appropriate course of action can be taken.

**What are the other side effects of the treatment received when taking part?**

The most common side effects from Spironolactone are diarrhoea, drowsiness, headache, nausea, stomach cramping and vomiting. Such effects are usually mild and temporary and resolve when the drug is stopped.

Other less common but serious side effects are severe allergic reactions (rash, hives, itching, difficulty breathing, tightness in the chest, swelling of the mouth, face, lips, or tongue), black, tarry, or bloody stools, change in the amount of urine produced, confusion, dark urine, decreased sexual ability, enlarged breasts in men, irregular or missed menstrual periods, severe or persistent stomach pain, symptoms of abnormal fluid or electrolyte levels (i.e.: fast, slow, or irregular heartbeat, increased thirst, muscle weakness, severe or persistent dry mouth, nausea, or vomiting, severe or persistent dizziness or drowsiness, unusual fatigue or sluggishness, tingling sensation), yellowing of the skin or eyes.

If you were to experience these serious side effects, **you should stop taking the trial medication immediately and contact our research team on 0800 9230329**.

**What are the benefits of taking part?**

Our previous research study showed that Spironolactone improves heart function and reduces hardening of the blood vessels in patients with mild kidney disease in our specialist hospital kidney clinic. However, we are unable to guarantee any direct benefit to you as a result of taking part in this study. Nonetheless, you will contribute to an improved understanding of Spironolactone and its effects on blood vessel and kidney disease. The

information gained from this study will also contribute to further studies and may help improve the treatment of people with kidney disease in the future.

**What if there is a problem?**

Any complaint about the way you have been dealt with during the study or any possible harm you might suffer will be addressed. The detailed information on this is given in Part 2.

**Will my taking part in the study be kept confidential?**

Yes. We will follow ethical and legal practice and all information about you will be handled in confidence. The details are included in Part 2.

**What will happen if I don't take part?**

Participation is entirely voluntary. If you decide not to take part then you will continue to be seen as before in outpatient clinics. A decision not to take part will not affect your routine care in any way.

**If the information in Part 1 has interested you and you are considering participation, please read the additional information in Part 2 before making any decision.**

**Part 2**

**What if relevant new information becomes available?**

Sometimes we get new information about the treatment being studied. If this new information means that we should stop the study, or change how we are running it, we will do this and make sure that you are offered the best treatment.

**What will happen if I do not want to carry on with the study?**

You are free to withdraw from the study at any time and this will not affect your care. You can either withdraw completely or choose to keep in contact with us to let us know your progress. Information collected earlier in the study may still be used.

**What if there is a problem?**

If you have concerns about any aspect of this study, you should ask to speak to the research coordinator who will do her best to answer your questions (contact numbers below).

If you remain unhappy and wish to complain formally, you can do this through the NHS Patient Advisory and Liaison Service (PALS) (Tel: 0800 389 8391; Email: pals@sbpct.nhs.uk). In the unlikely event that something does go wrong and you are harmed during the research and this is due to someone's negligence then you may have grounds for compensation against the University of Birmingham but you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you.

**Will my taking part in the study be confidential?**

Yes. We will follow ethical and legal practice and all information about you will be handled in confidence. The study information will only be seen by the research team and will be stored in accordance with the Data Protection Act at the University of Birmingham. The

study data may also be looked at by representatives of regulatory authorities and by authorized people to check that the study is being carried out correctly. All those associated with the study will have a duty of confidentiality to you as a research participant.

**Will my GP be told that I am in a study?**

Yes, we will inform your GP of your involvement in the study.

**What will happen to any samples I give?**

During study visits, extra blood and urine samples will be taken from you. These will be labelled with your study number. These samples will be anonymised and kept in a locked secure room within the University of Birmingham. Access will be restricted to the study researchers only. At the end of the study, these extra samples will be kept for 5 years and might be used for other future ethically approved studies.

**Will any genetic tests be done?**

No genetic tests will be performed.

**What will happen to the results of the research study?**

The results of the research will be published in international, peer-reviewed scientific journals. The results will also be available on the website www.clinicaltrials.gov. You will not be identifiable in any report or publication.

**Who is organising and funding the research?**

**The study is organised by the Primary Care Clinical Research and Trials Unit (PC-CRTU) at the University of Birmingham and is funded by the National Institute for Health Research.**

**Who has reviewed the study?**

Before deciding whether to fund the study, the National Institute for Health Research asked the opinion of independent expert. This study has also been reviewed and approved by West Midlands Research Ethics Committee.

**What if I have more questions or do not understand something?**

We will be pleased to answer any questions you may have or clarify things you do not understand. You can contact the STOP-CKD team on Tel: **0800 9230329**

If you wish to discuss the study with a doctor who is not directly involved with the study you may contact Dr Lukas Foggensteiner on Tel: 0121 371 5841.

**What happens now if I decide to take part?**

If you decide that you would like to participate in this study, we ask you to complete the attached form with your details and send it back to us in the envelope provided. You may also contact us by telephone or e-mail to inform us of your decision to participate. The STOP-CKD research team will then contact you to arrange a convenient day to attend your GP surgery.

Please return to:
STOP-CKD Research Team,
Primary Care Clinical Research and Trial Unit,
University of Birmingham
Edgbaston
Birmingham
B15 2TT

Dear Dr Ferro

Name: …… Tel: ……
Address:…… Mobile: .....
……
…… Postcode: .....

Signature: …… Date: __ __/__ __/__ __ __ __

Please tick if applicable:

□ **I am interested in participating in this study. I would be happy for a member of the study team to contact me to arrange a date to attend.**

□ **I do NOT wish to be involved in this study.**

*If you have decided **not** to take part in this study, it would be very useful if you could tell us your reasons to help us to improve other research studies in the future. We would be grateful if you could complete the following **voluntary** questionnaire and return it in the enclosed prepaid envelope:*

I am: Male ☐ Female ☐ My date of birth is: __ __/__ __/__ __ __ __

I do not wish to take part in this study for the following reason(s): *Tick as many as applicable*

□ I do not have time to take part in the study
□ I do not wish to take a new medication
□ I do not wish to have further blood tests
□ I do not wish to be part of a research trial
□ Kidney problems are of no concern to me
□ I am unable to attend the surgery
□ I do not want to give a reason
□ Other (Please specify): ……

Please tick if applicable:

□ **I am interested to take part in an INTERVIEW study to discuss my reasons further**

*We are carrying out a separate interview study to find out people's view of research study in kidney disease in the community. If you are interested, we will send out further information on the INTERVIEW study to you.*

□ **I am NOT interested to take part in an INTERVIEW study to discuss my reasons further**

If you wish to give further information, please do so below:

……

……

……

Appendix 4-4: STOP-CKD Part 1 Consent Form

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Site ID: | | | | | | | |
| Patient ID: | | | | | | | |
| Patient Initials: | | | | | | | |

UNIVERSITY OF BIRMINGHAM

**STOP-CKD**

**Spironolactone to Prevent Cardiovascular Events in Early Stage Chronic Kidney Disease: A Pilot Trial**

**Patient Consent Form (Part 1)** Version 2.2 20/06/2013

**Please initial each box if you agree with the statement:**

1. I confirm that I have read and understood the information sheet dated 20/06/2013 (version 2.2) for the above study. I have had the opportunity to consider the information, to ask questions and have had these answered satisfactorily. ☐
2. I give permission for my name to be given to the trials office when I am registered on the STOP-CKD study and for movement of my personal data from my GP Practice to the University of Birmingham. ☐
3. I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from the sponsor, regulatory authorities or from University of Birmingham where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. However, I understand that I will not be identified by name in any reports or publications resulting from this study. ☐
4. I agree to donate an initial blood and urine sample for lab testing to determine eligibility for the study and understand that I may not be suitable to take part as detailed in the information sheet. I agree that samples taken will be stored for the duration of the study and 5 years after the end of the study which may be used for other future ethically approved studies. ☐
5. I agree to my GP being informed of my participation in the study ☐
6. I understand that my participation is voluntary and that I am free to withdraw at any time without giving a reason without my medical or legal rights being affected. I agree to take part in the above study ☐

| | | |
|---|---|---|
| ..... | ..... | ..... |
| Name of patient | Date | Signature |
| ..... | ..... | ..... |
| Name of person taking consent | Date | Signature |
| ..... | ..... | ..... |
| Name of Researcher | Date | Signature |

3 copies: 1 for patient; 1 for researcher site file; 1 for medical notes

Appendix 4-5: STOP-CKD Part 2 Consent Form

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Site ID:** | | | | | | | |
| **Patient ID:** | | | | | | | |
| **Patient Initials:** | | | | | | | |

**STOP-CKD**

**S**pironolactone **to** **P**revent **C**ardiovascular Events in Early Stage **C**hronic **K**idney **D**isease: A Pilot Trial

**Patient Consent Form (Part 2)** Version 2.2 20/06/2013

**Please initial each box if you agree with the statement:**

1. I confirm that I have read and understood the information sheet dated 20/06/2013 (version 2.2) for the above study. I have had the opportunity to consider the information, to ask questions and have had these answered satisfactorily. ☐
2. I give permission for my name to be given to the trials office when I am registered on the STOP-CKD study and for movement of information collected about me for the trial from my GP Practice to the University of Birmingham. ☐
3. I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from the sponsor, regulatory authorities or from University of Birmingham where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. However, I understand that I will not be identified by name in any reports or publications resulting from this study. ☐
4. I understand participation in this study is a 46 weeks commitment. I agree to attend clinics and donate blood and urine samples for study as detailed in the information sheet. I agree that samples taken will be stored for the duration of the study and 5 years after the end of the study which may be used for other future ethically approved studies. ☐
5. I understand that only specific pharmacies have been recruited to participate in the study and I agree to be directed to these pharmacies to obtain the trial medication prescribed. ☐
6. I agree to my GP being informed of my participation in the study. ☐
7. I understand that my participation is voluntary and that I am free to withdraw at any time without giving a reason without my medical or legal rights being affected. I agree to take part in the above study. ☐

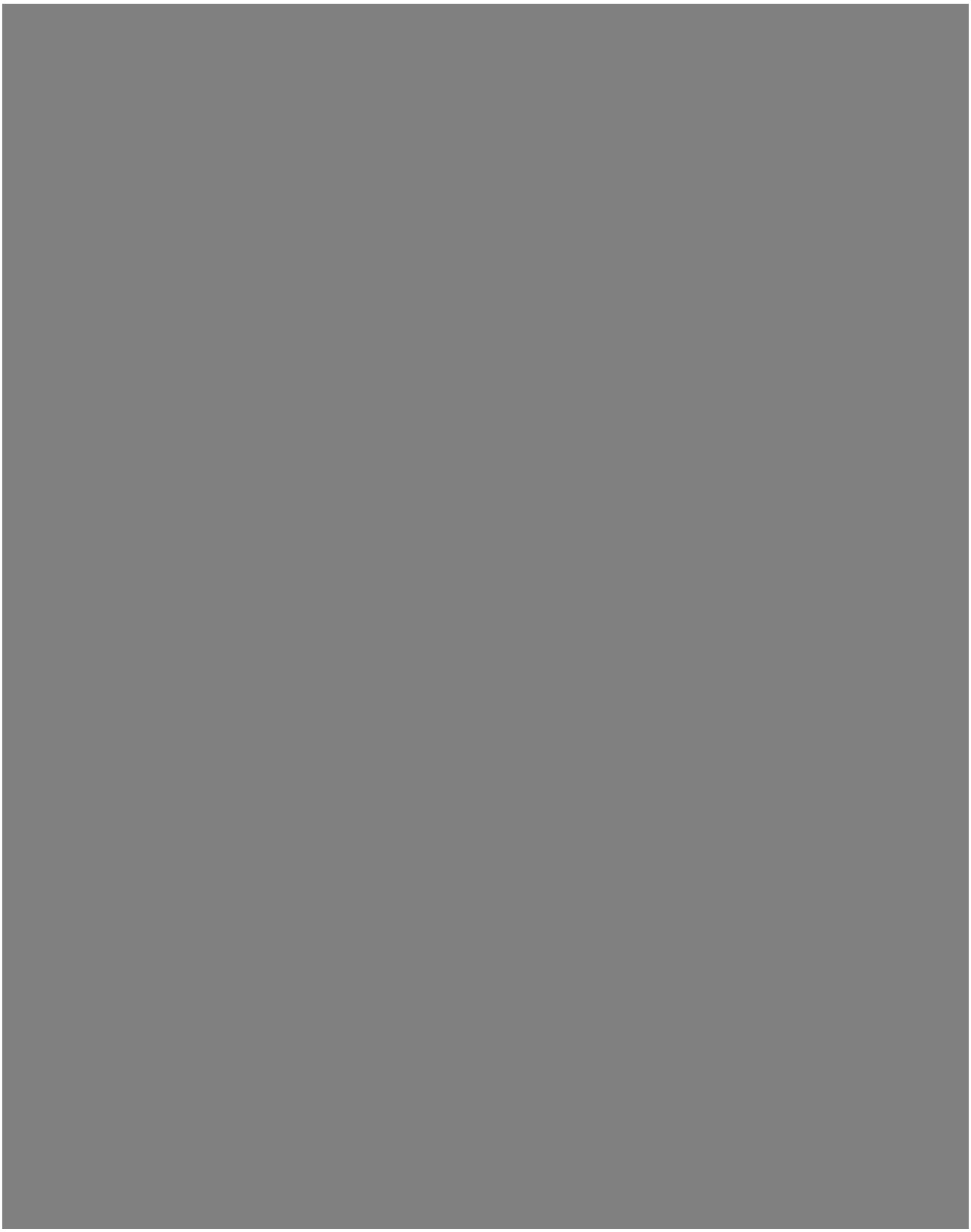
| | | |
|---|---|---|
| ..... | ..... | ..... |
| Name of patient | Date | Signature |
| ..... | ..... | ..... |
| Name of person taking consent | Date | Signature |
| ..... | ..... | ..... |
| Name of Researcher | Date | Signature |

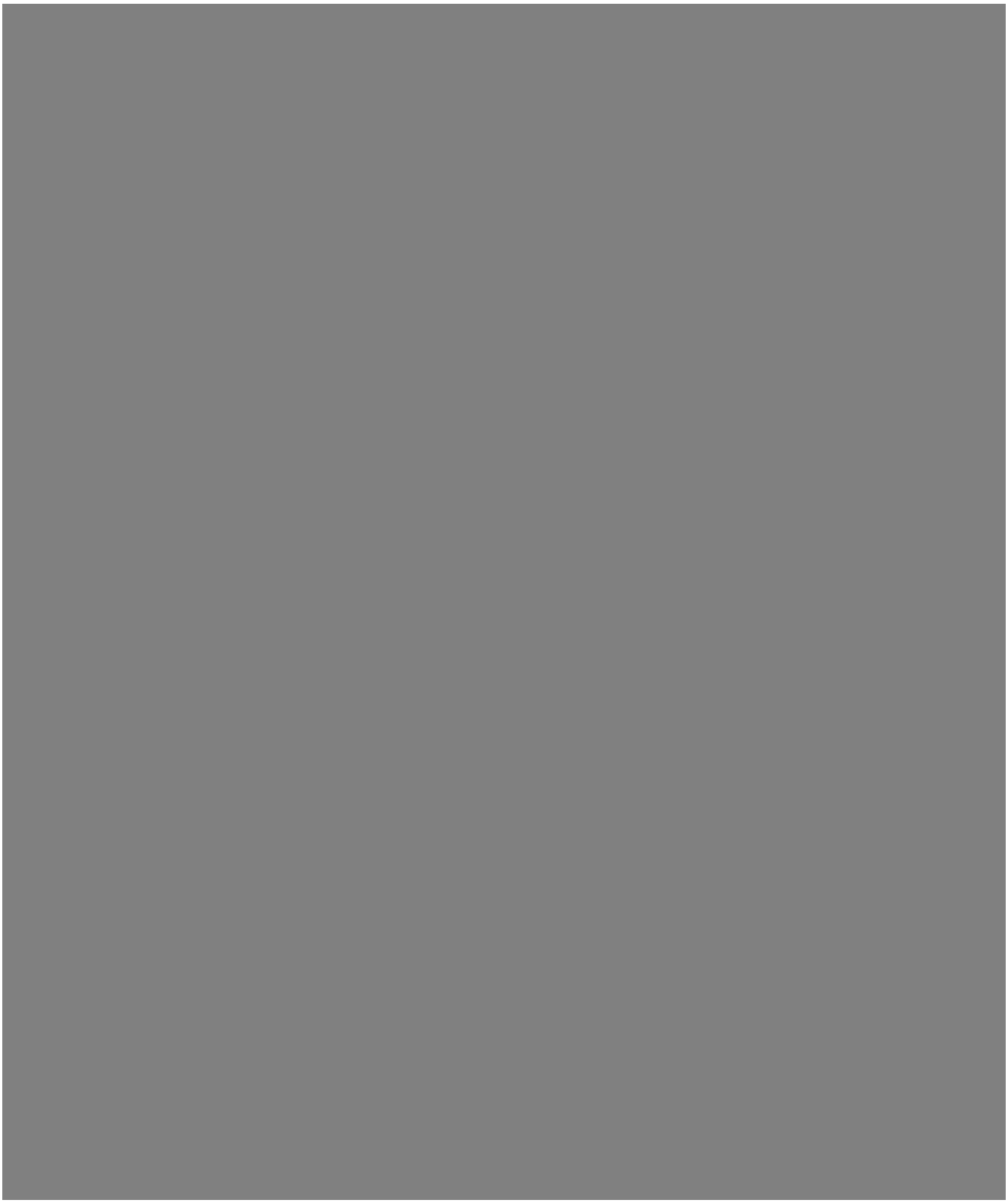
3 copies: 1 for patient; 1 for researcher site file; 1 for medical notes

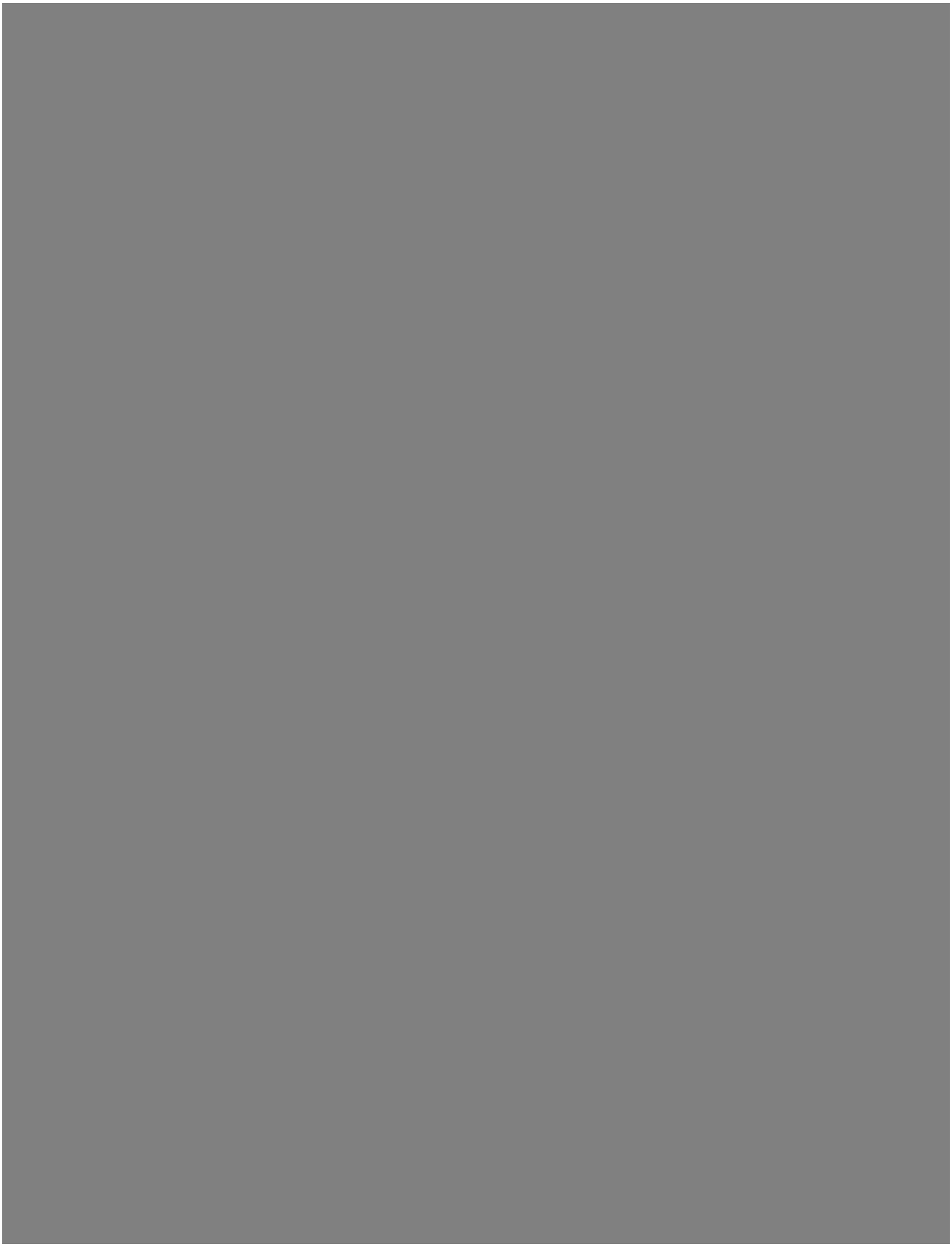
Appendix 4-6: STOP-CKD medication monitoring questionnaire

| **Side Effect** | **Yes** | **No** |
|---|---|---|
| Nausea | | |
| Vomiting | | |
| Abdominal Discomfort | | |
| Diarrhoea | | |
| Black Discoloured Stool | | |
| Tiredness | | |
| Headache | | |
| Confusion | | |
| Drowsiness | | |
| Dizziness/ Imbalance | | |
| Breast swellings | | |
| Breast pain | | |
| Menstrual (period) disturbance | | |
| Change in libido | | |
| Excessive hair growth | | |
| Unwanted hair growth | | |
| Hair loss | | |
| Leg cramps | | |
| Rash | | |
| Joint pain | | |
| Others: (Please comment) | | |

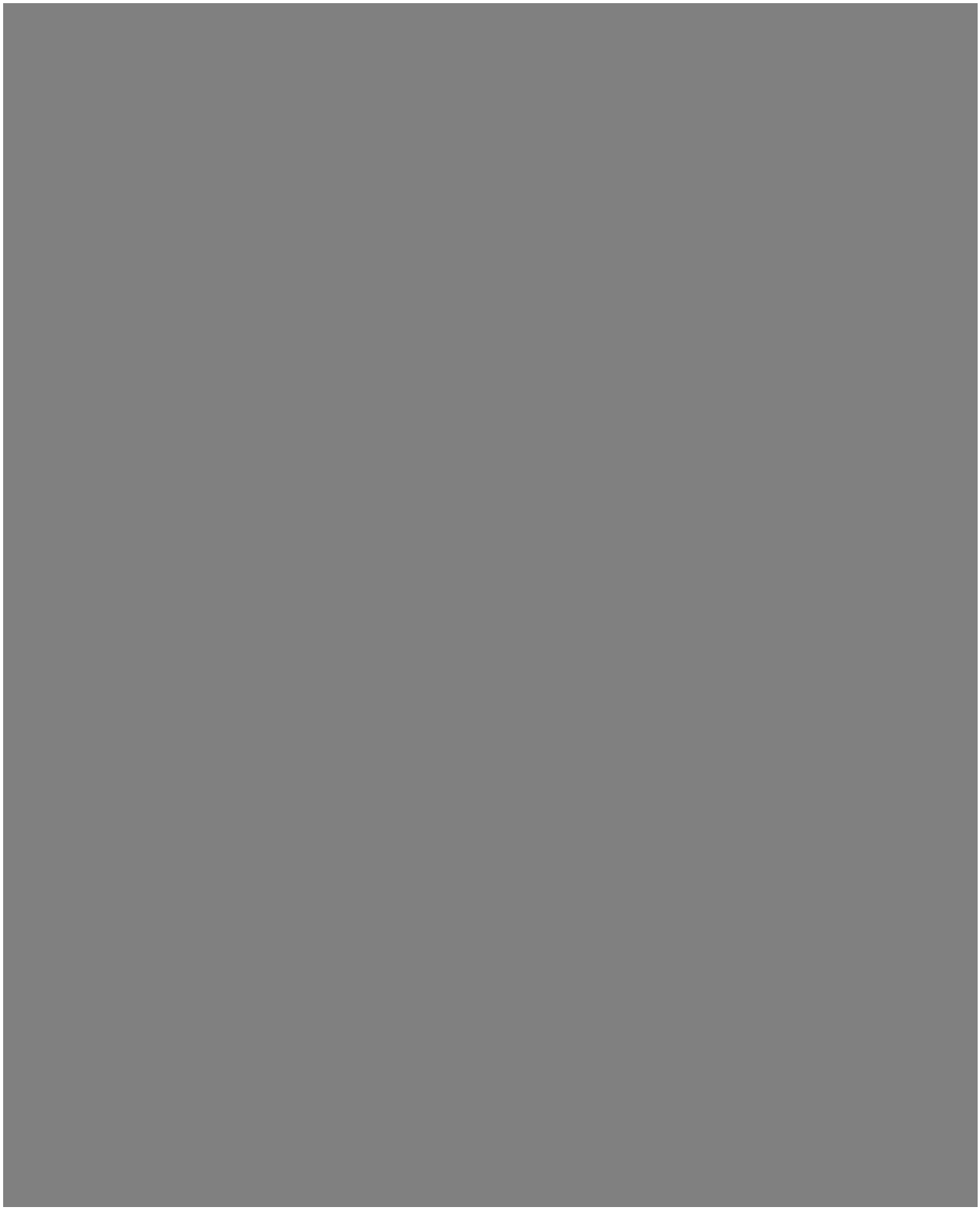
Appendix 4-7: STOP-CKD study abnormal blood pressure working instruction

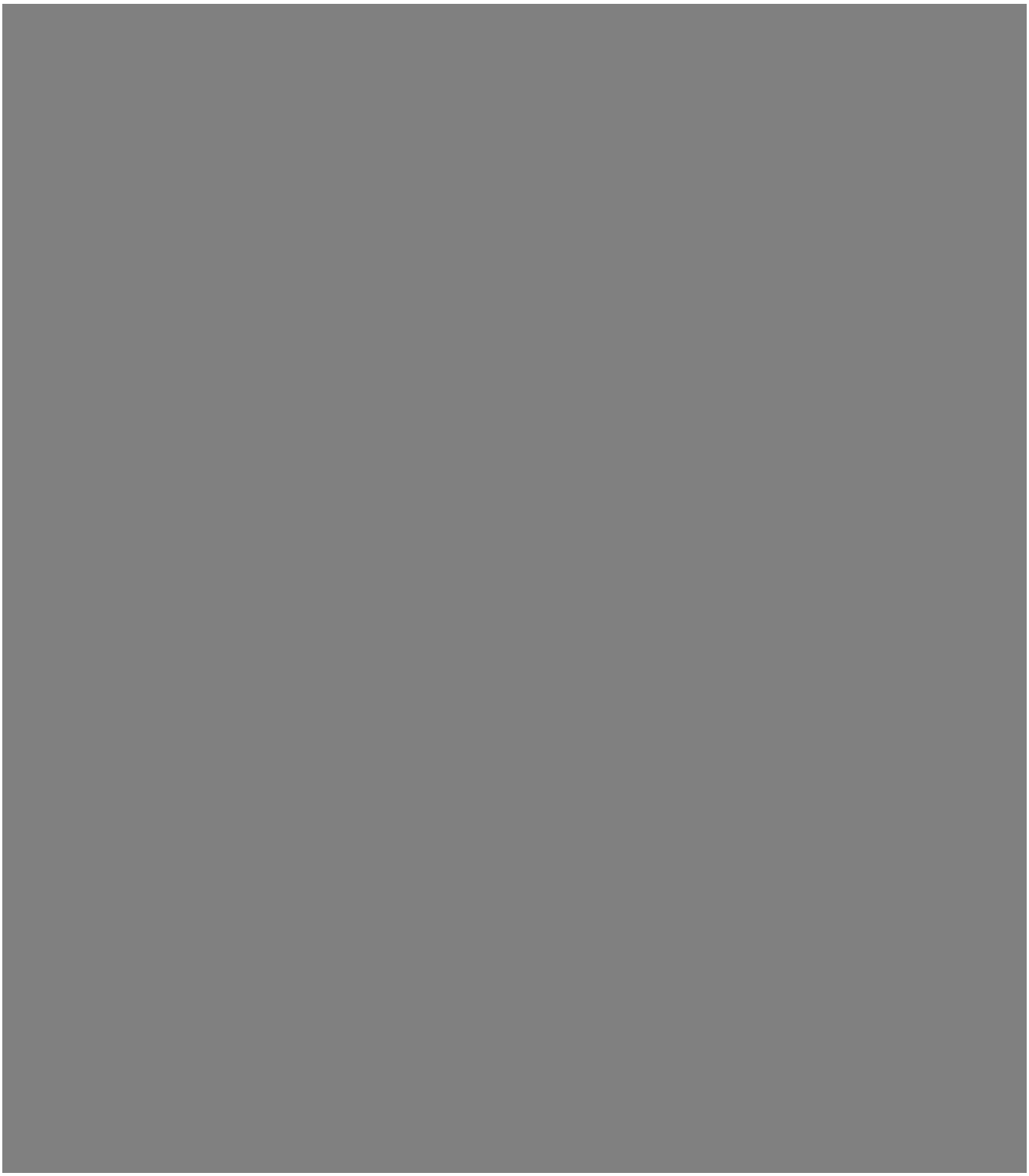


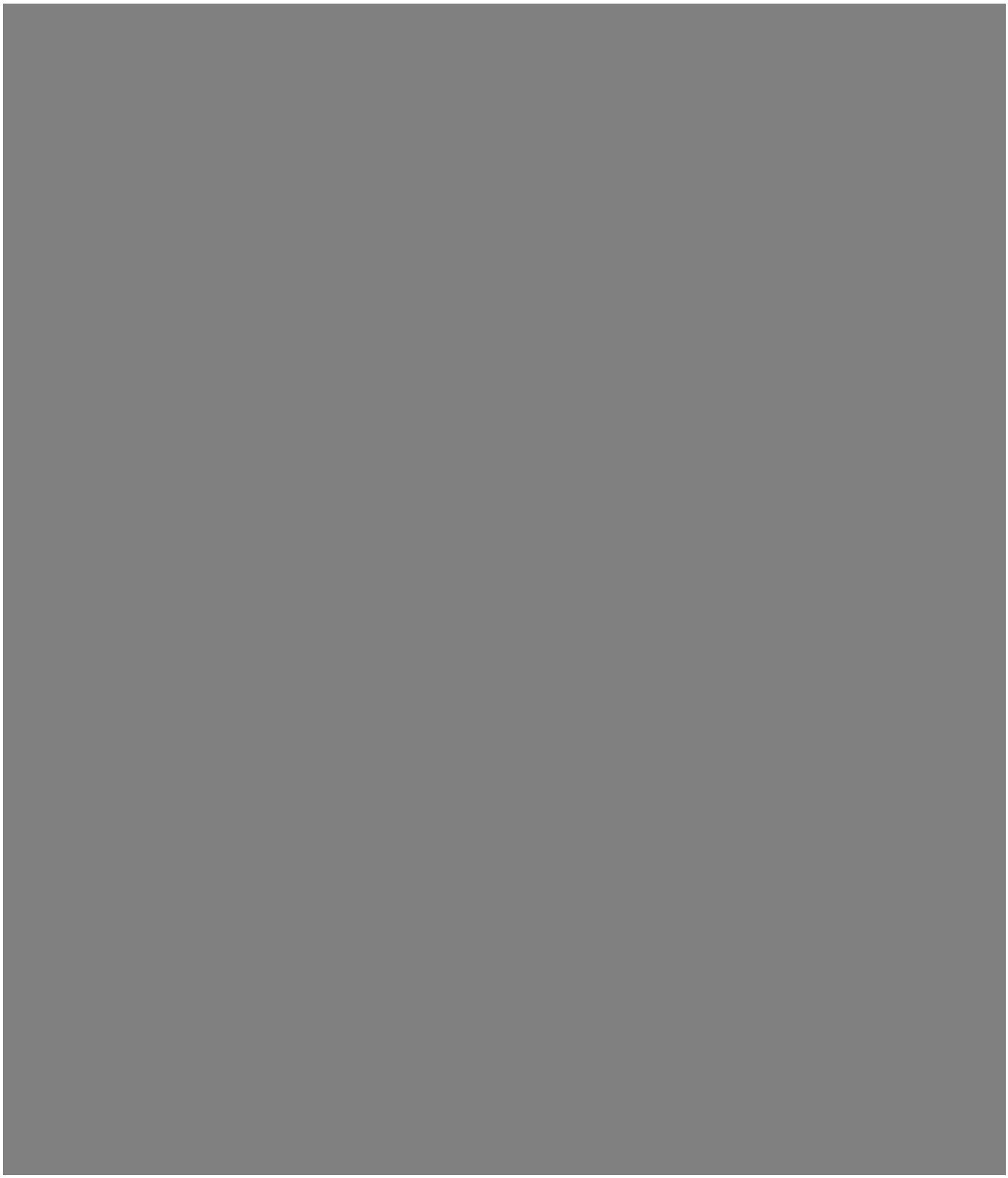


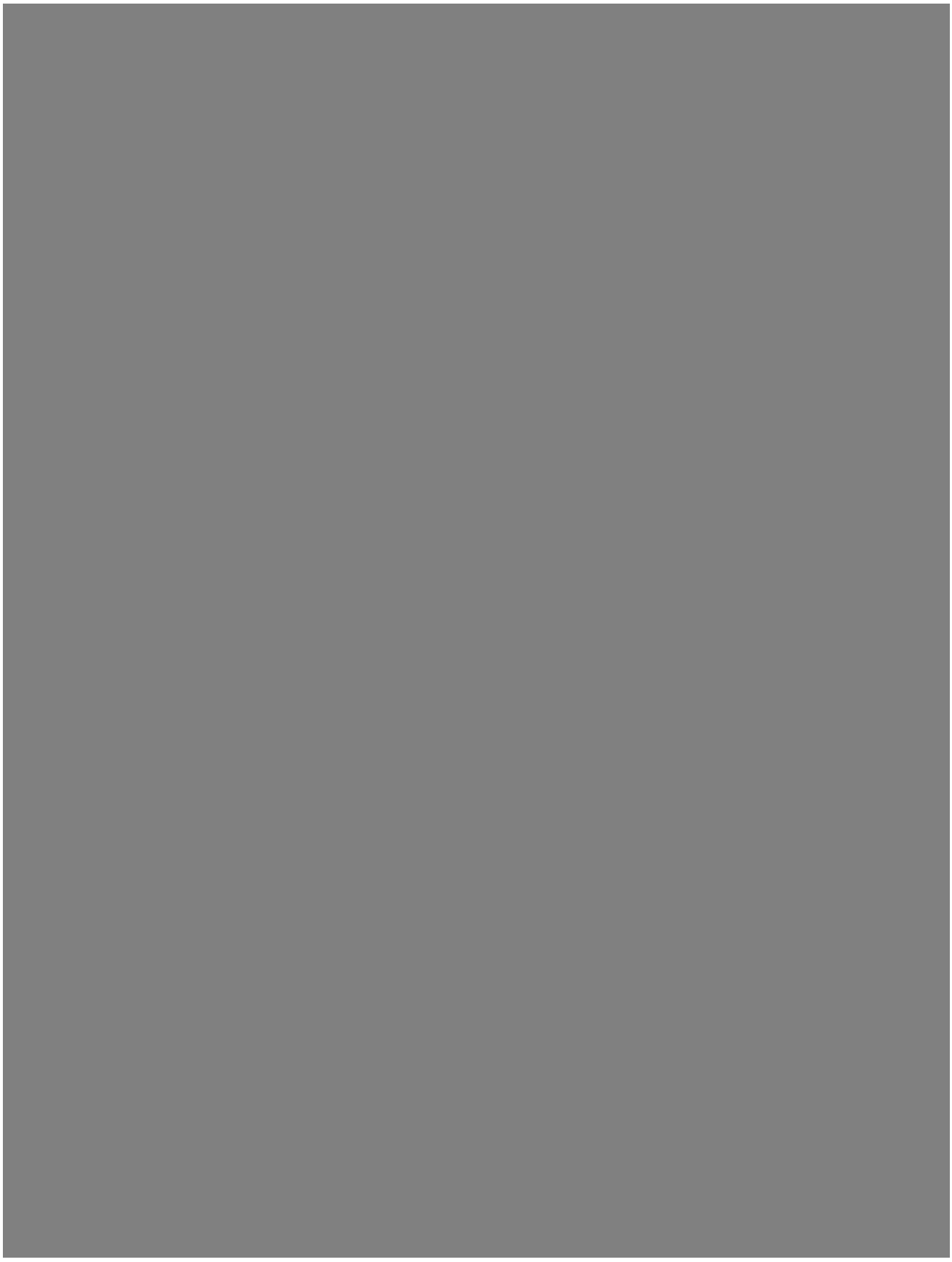


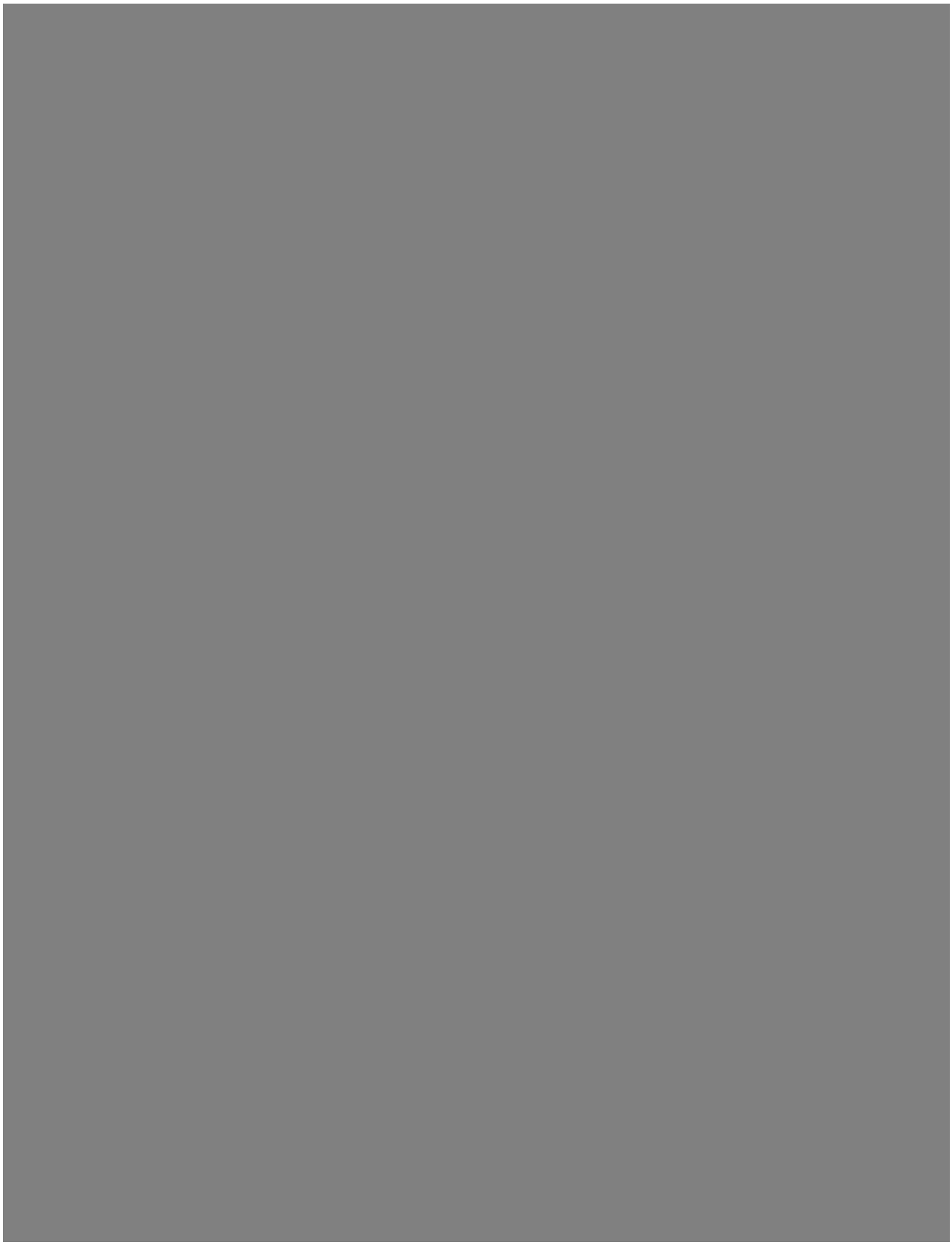
Appendix 4-8: STOP-CKD working instruction on the use of BpTRU blood pressure monitor

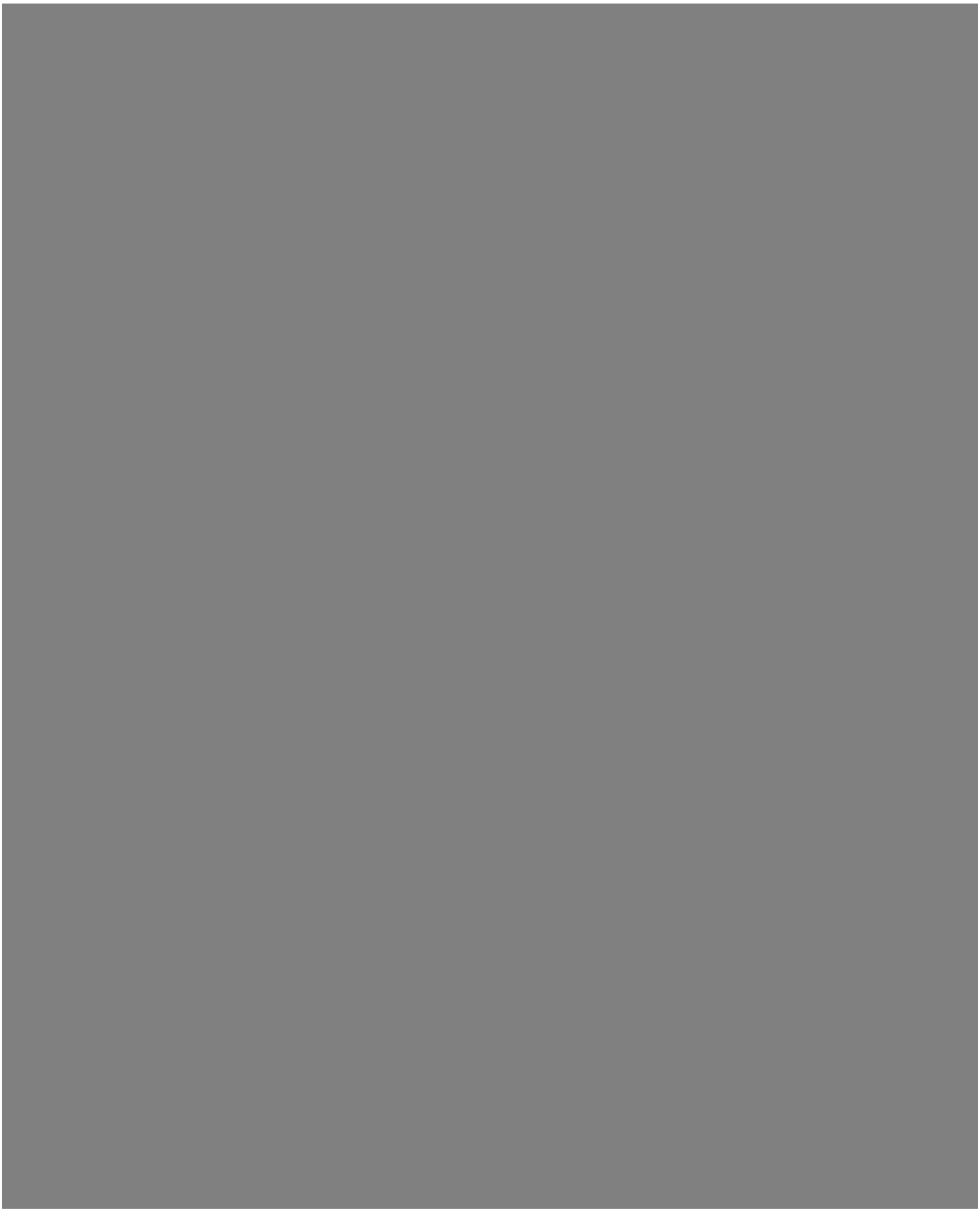




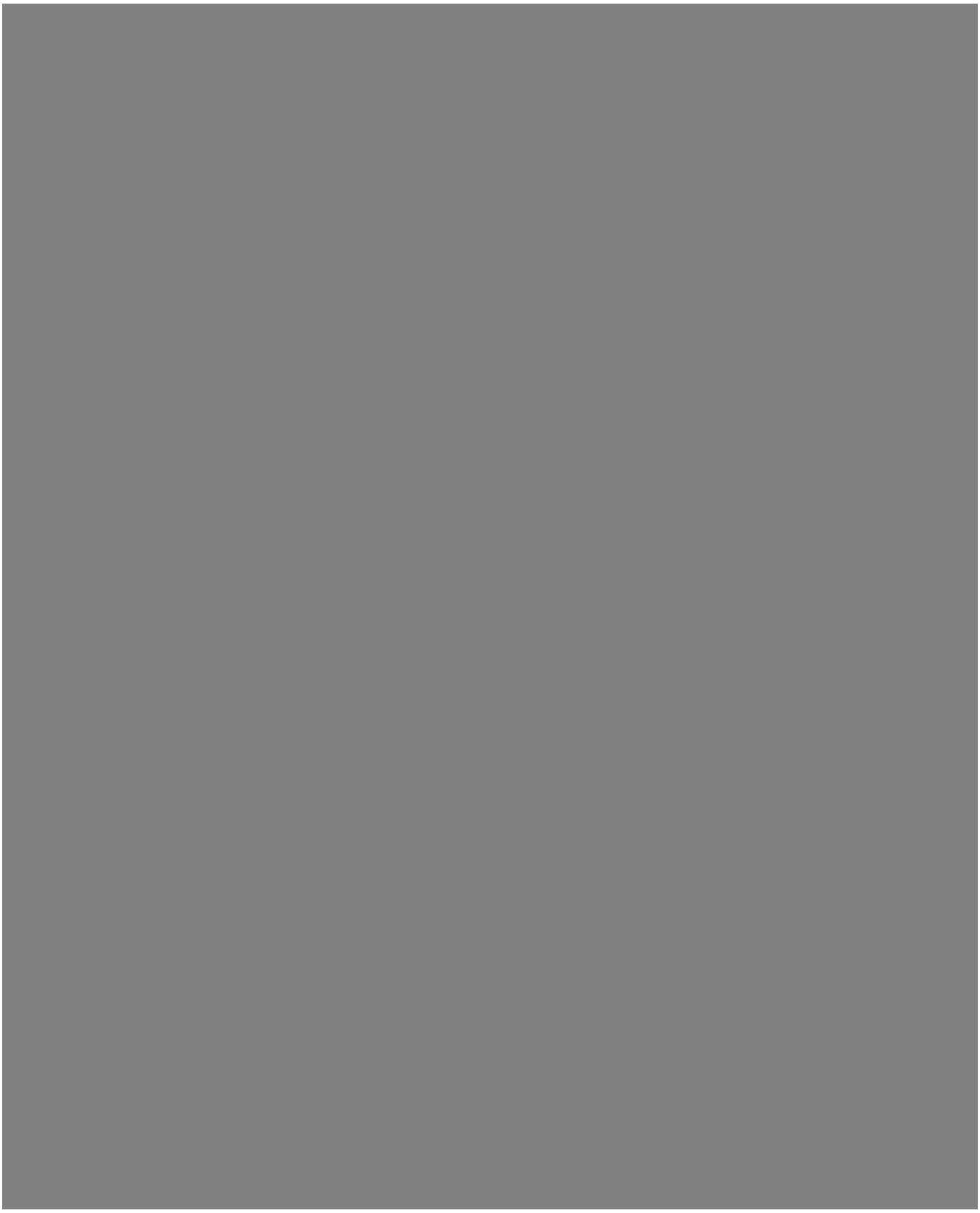


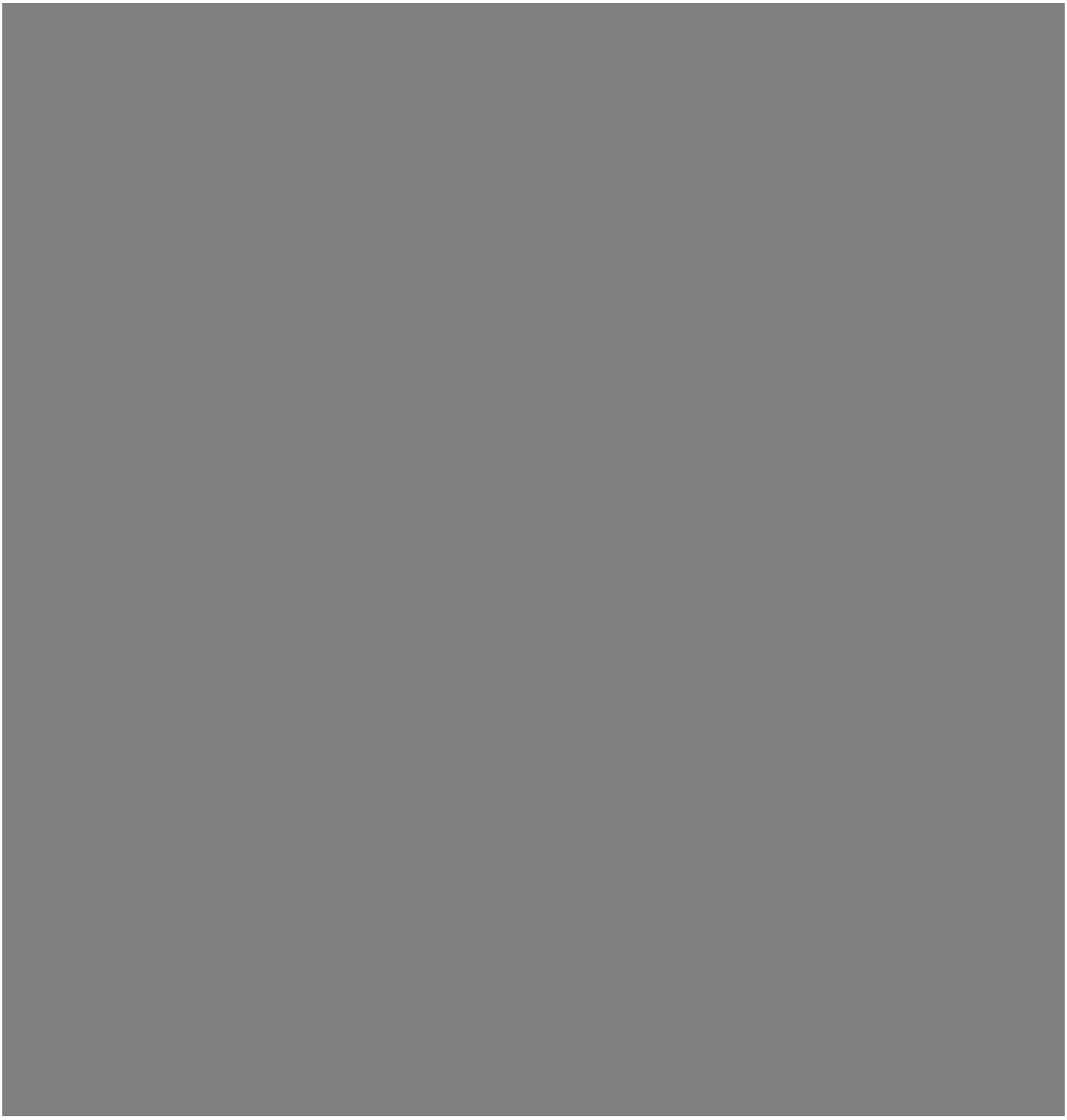


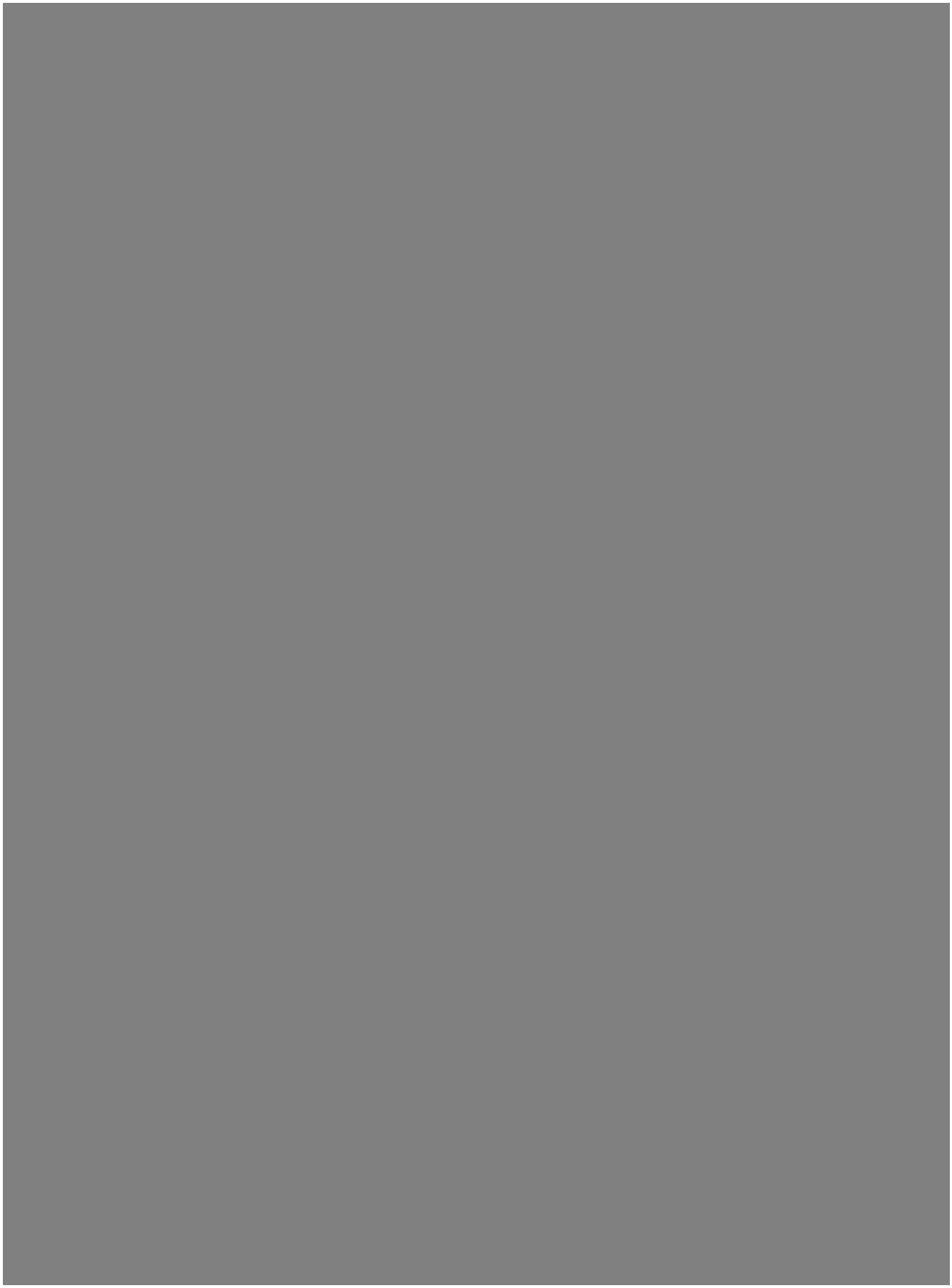


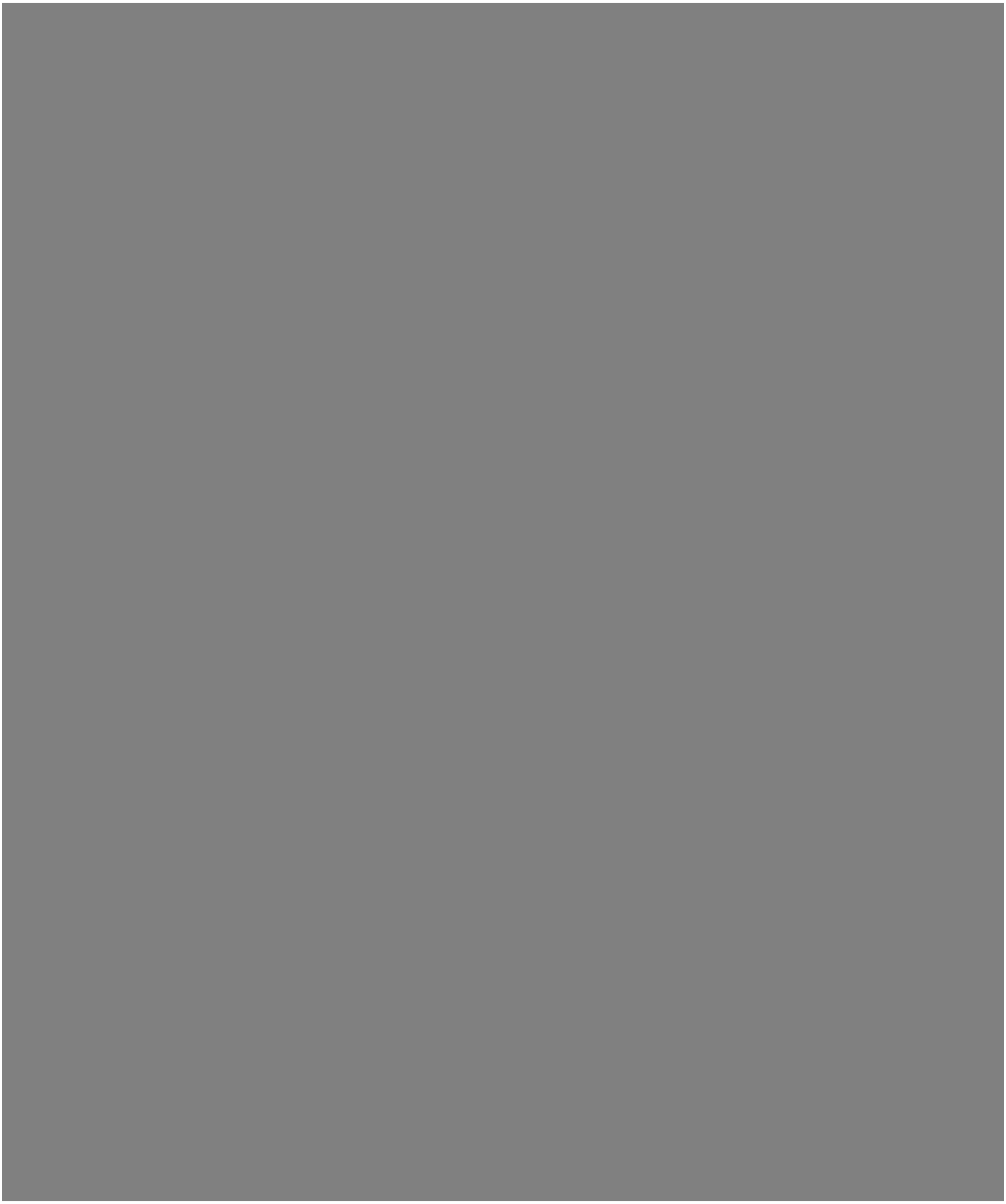


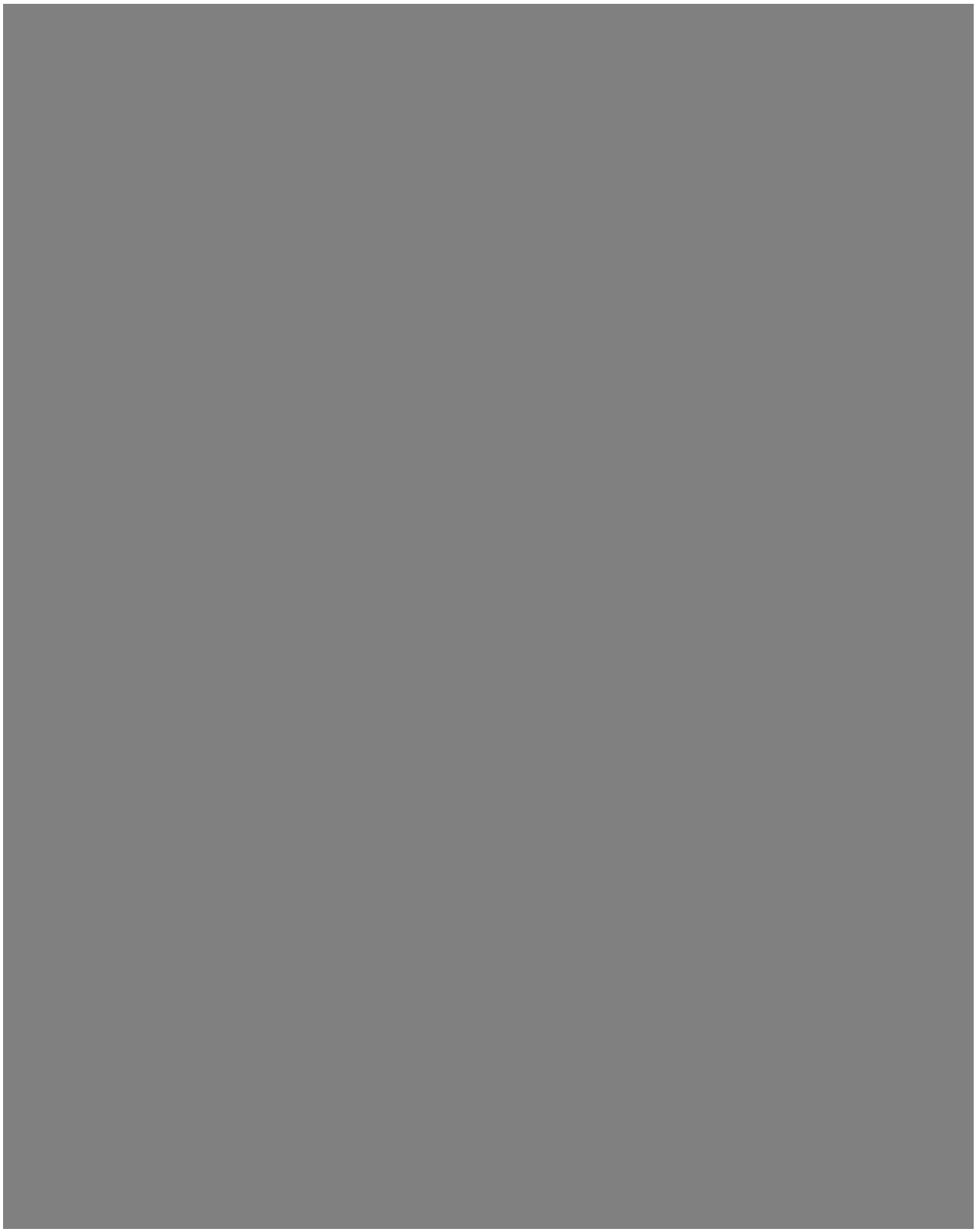
Appendix 4-9: STOP-CKD working instruction on the use of Vicorder system for the measurement of PWV and PWA

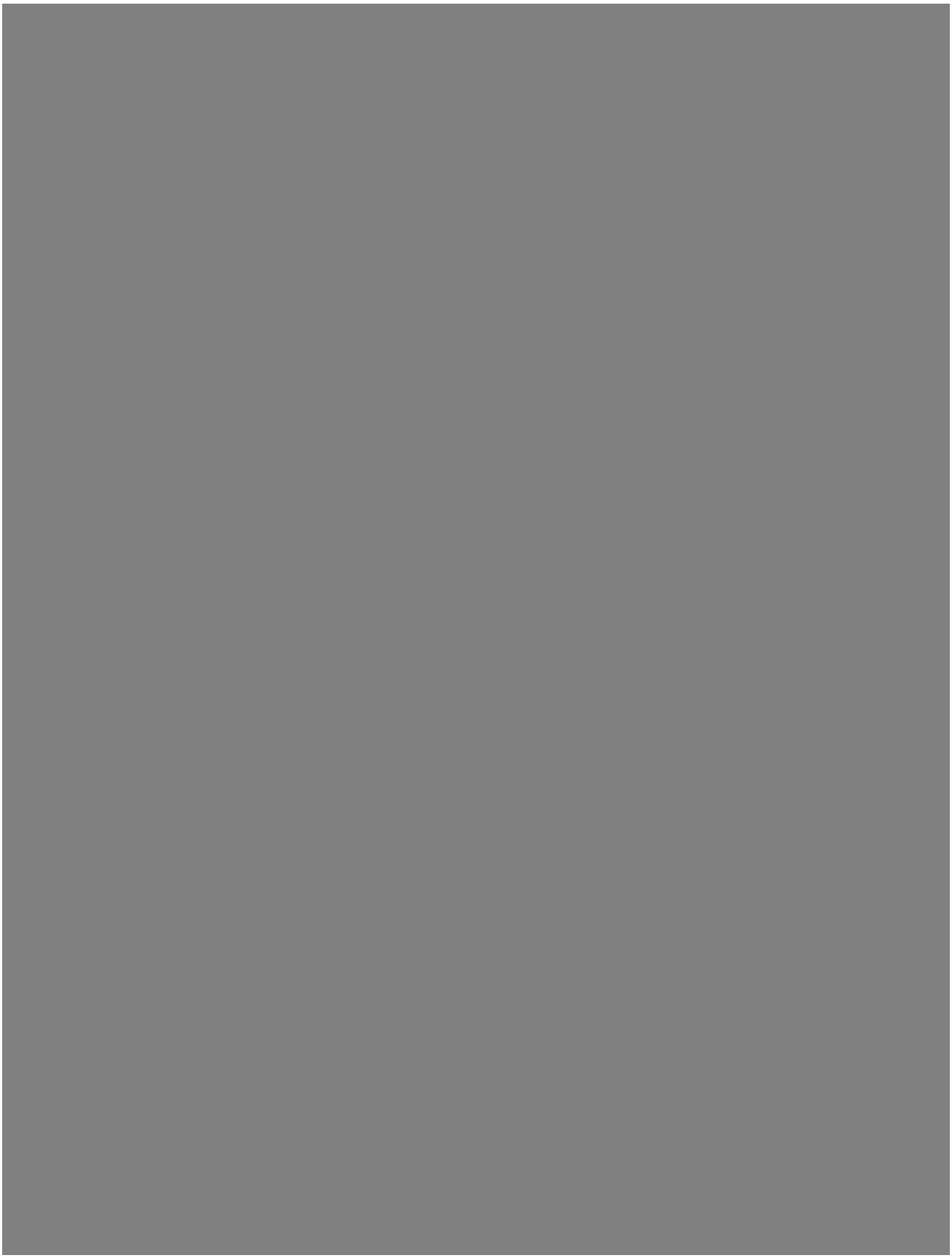


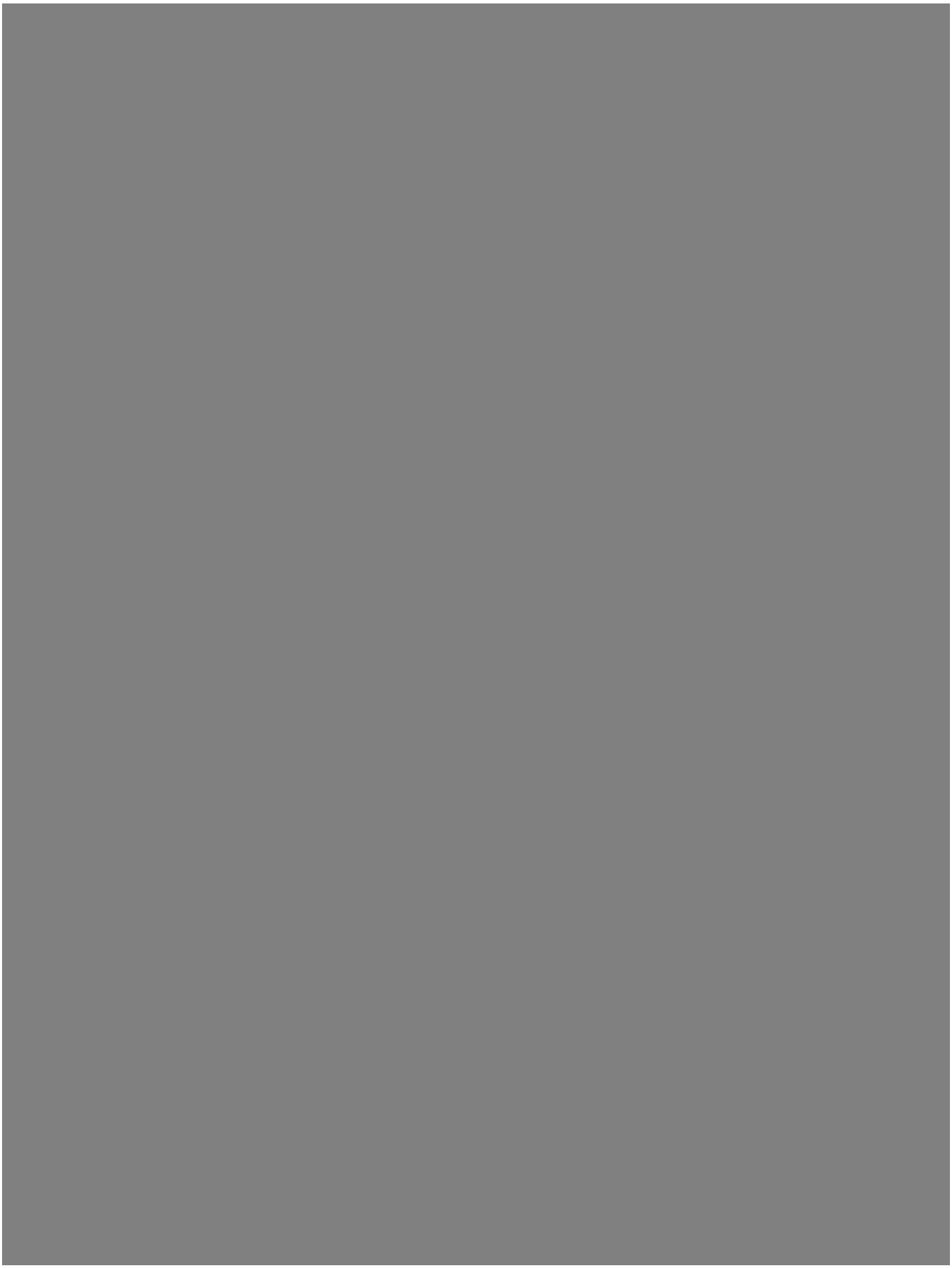


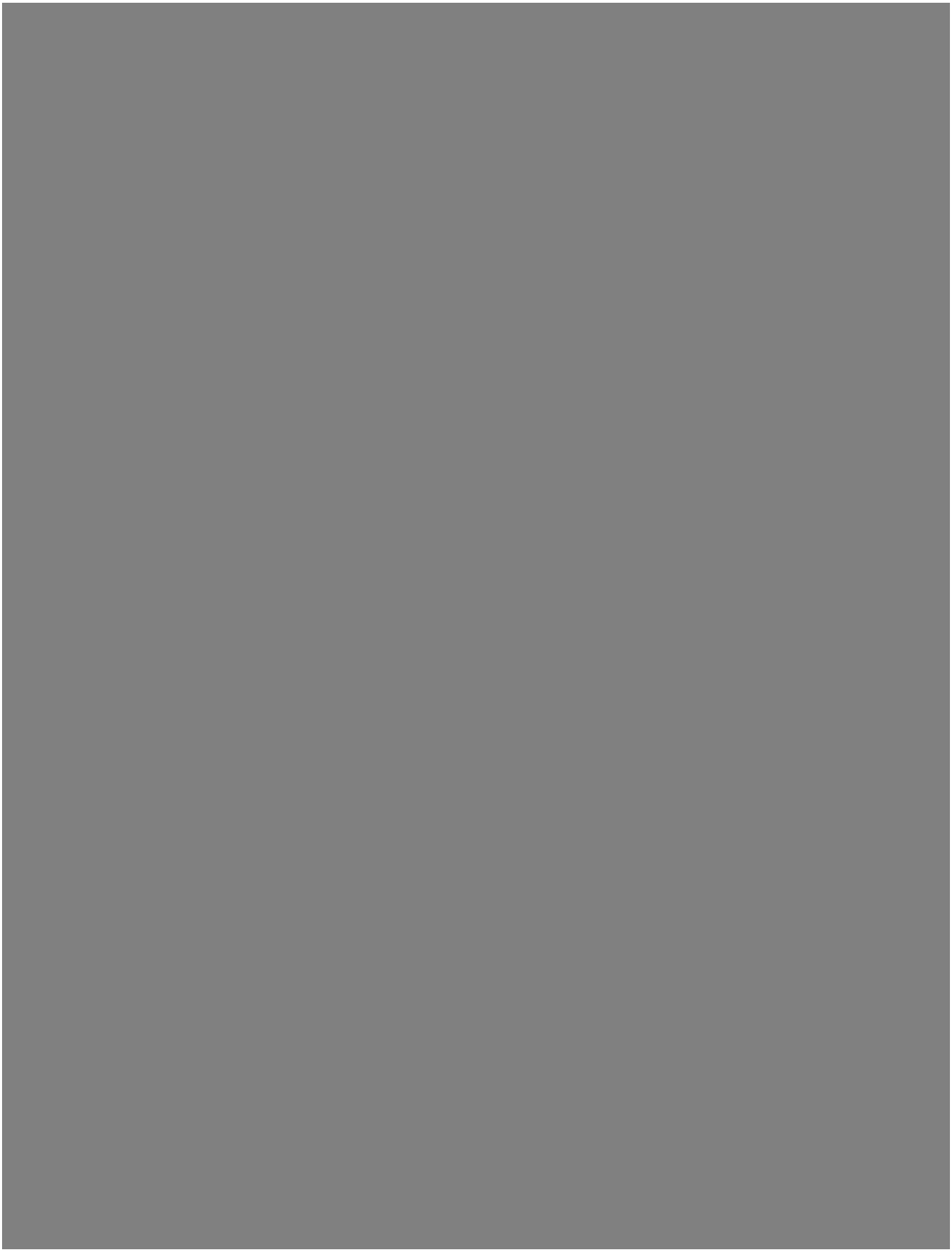


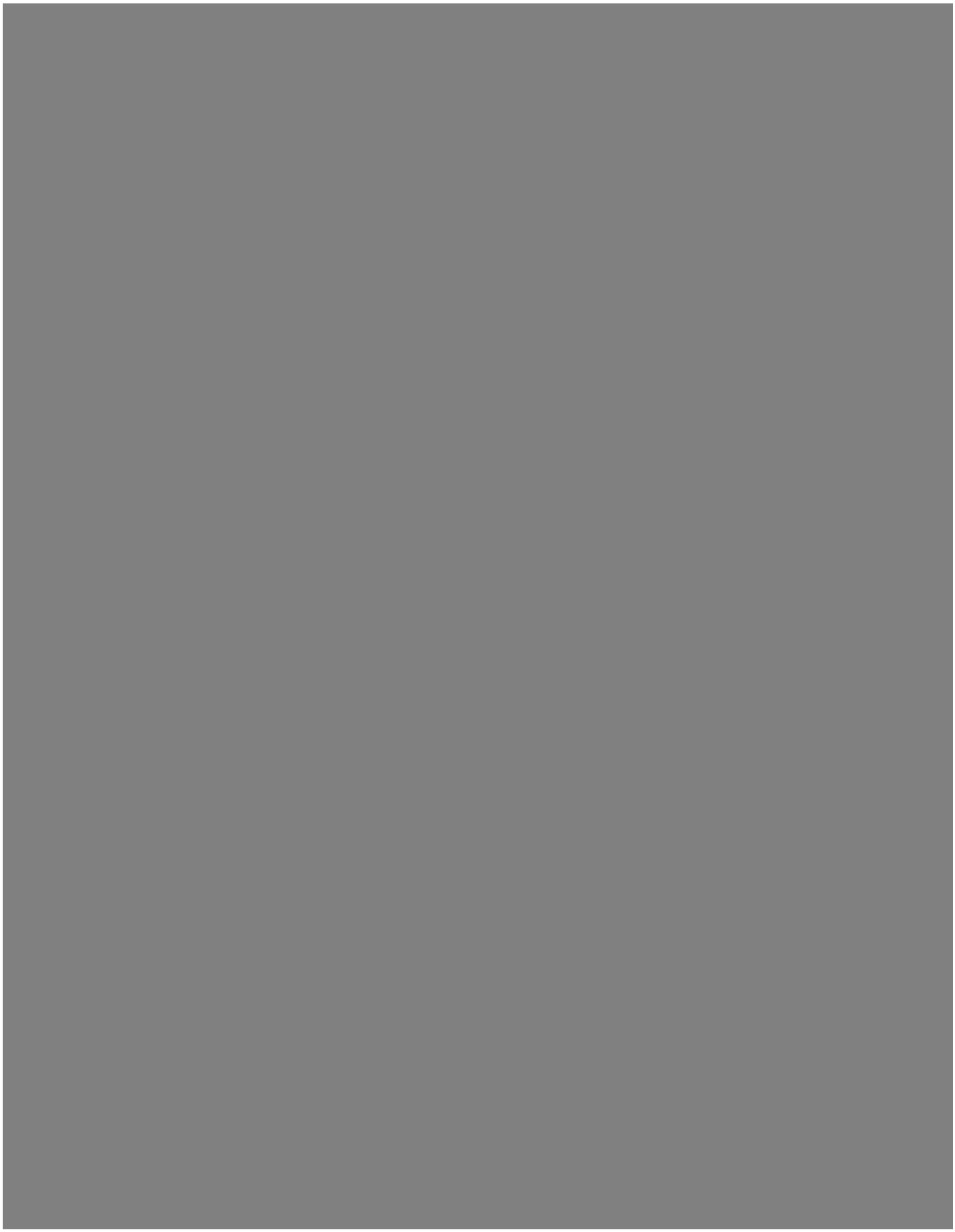








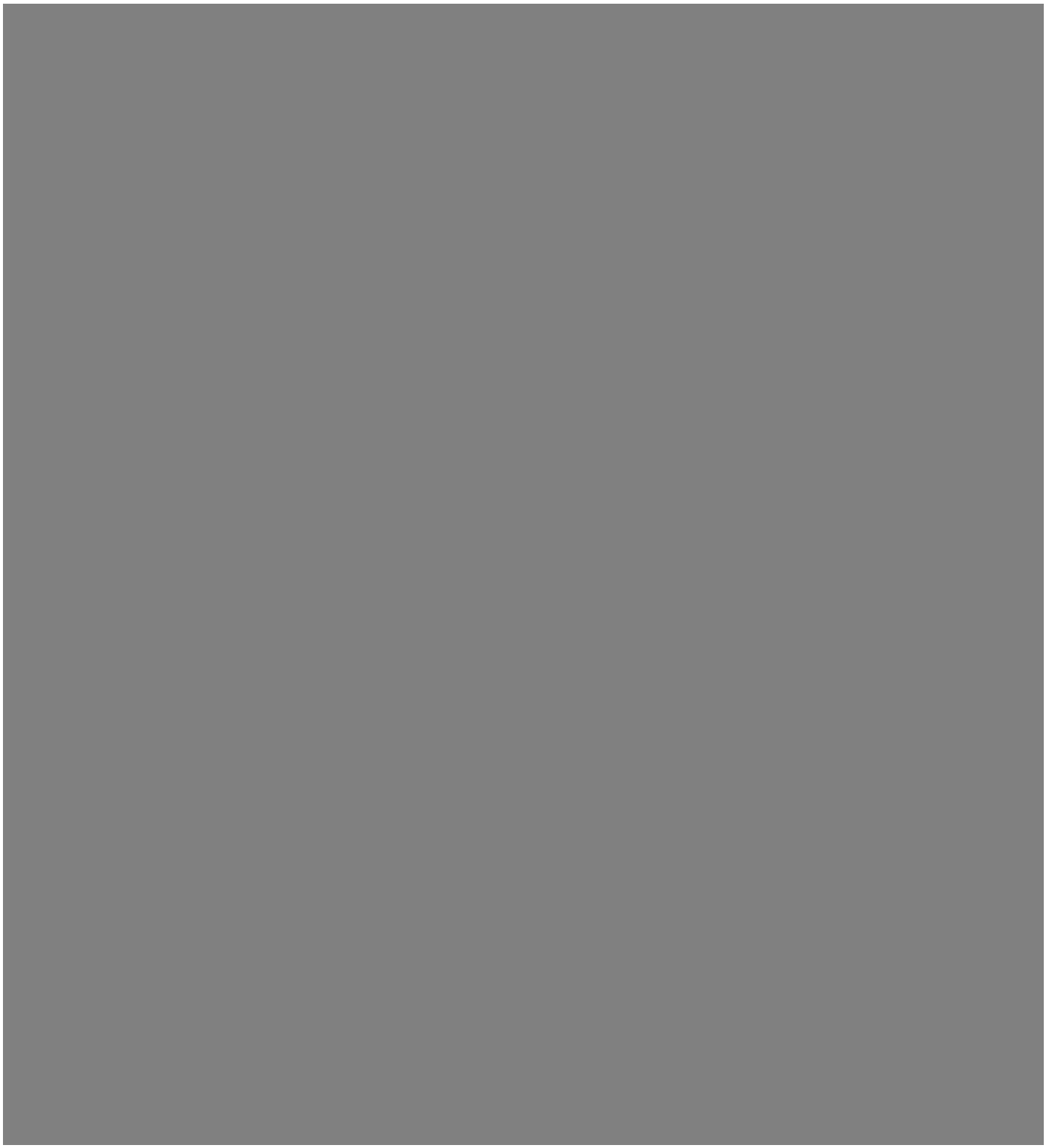


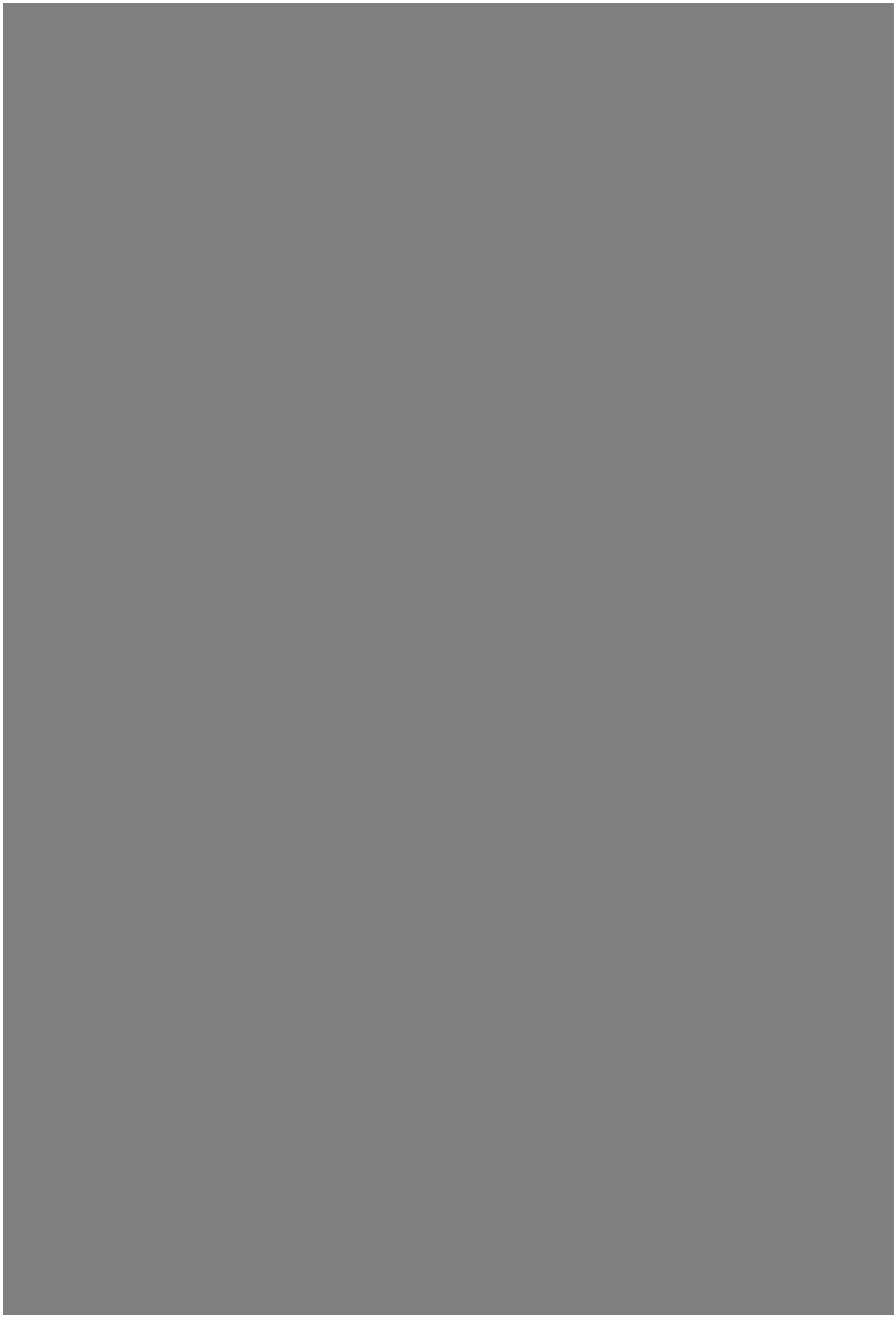


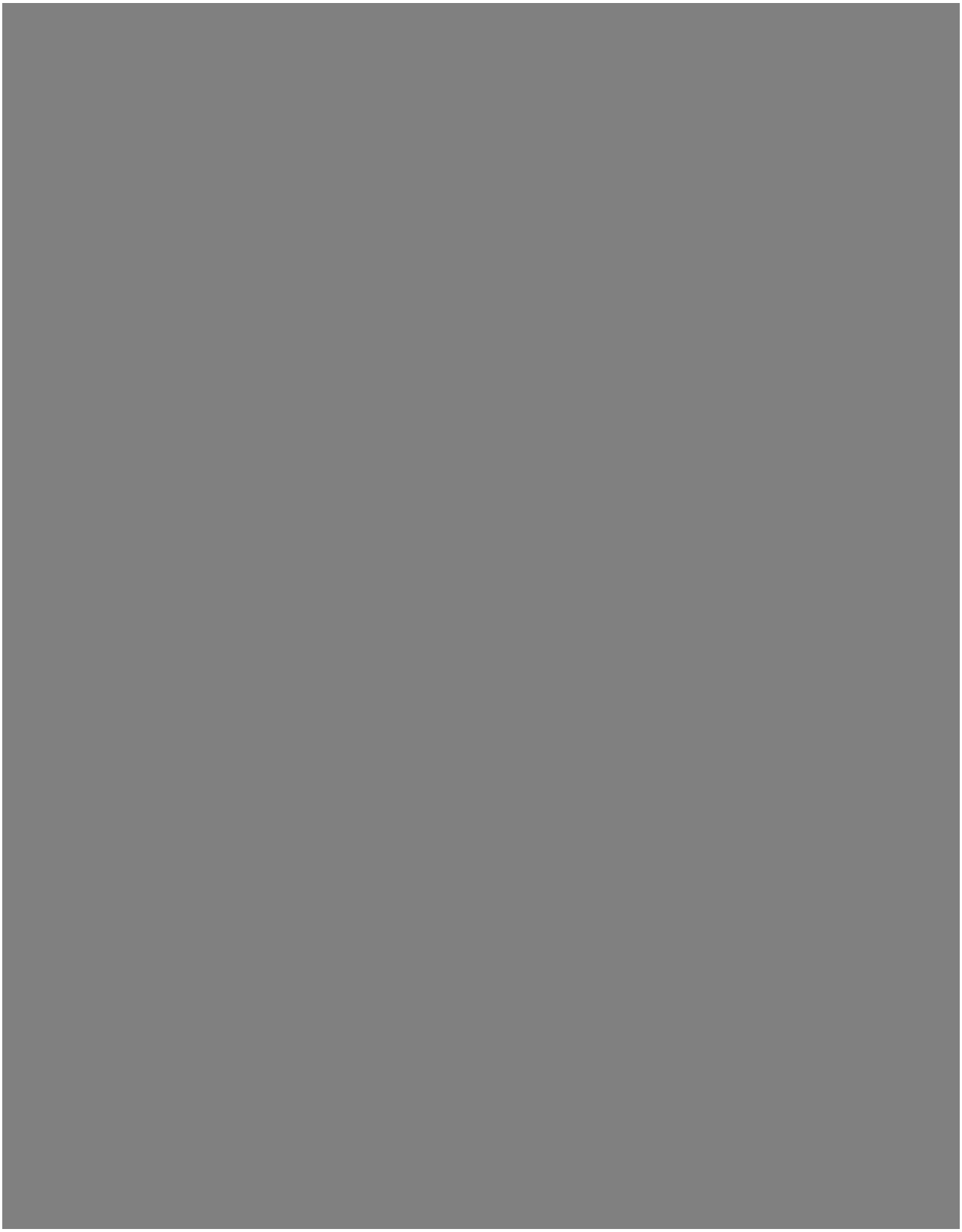
Appendix 4-10: STOP-CKD Trial Steering Committee

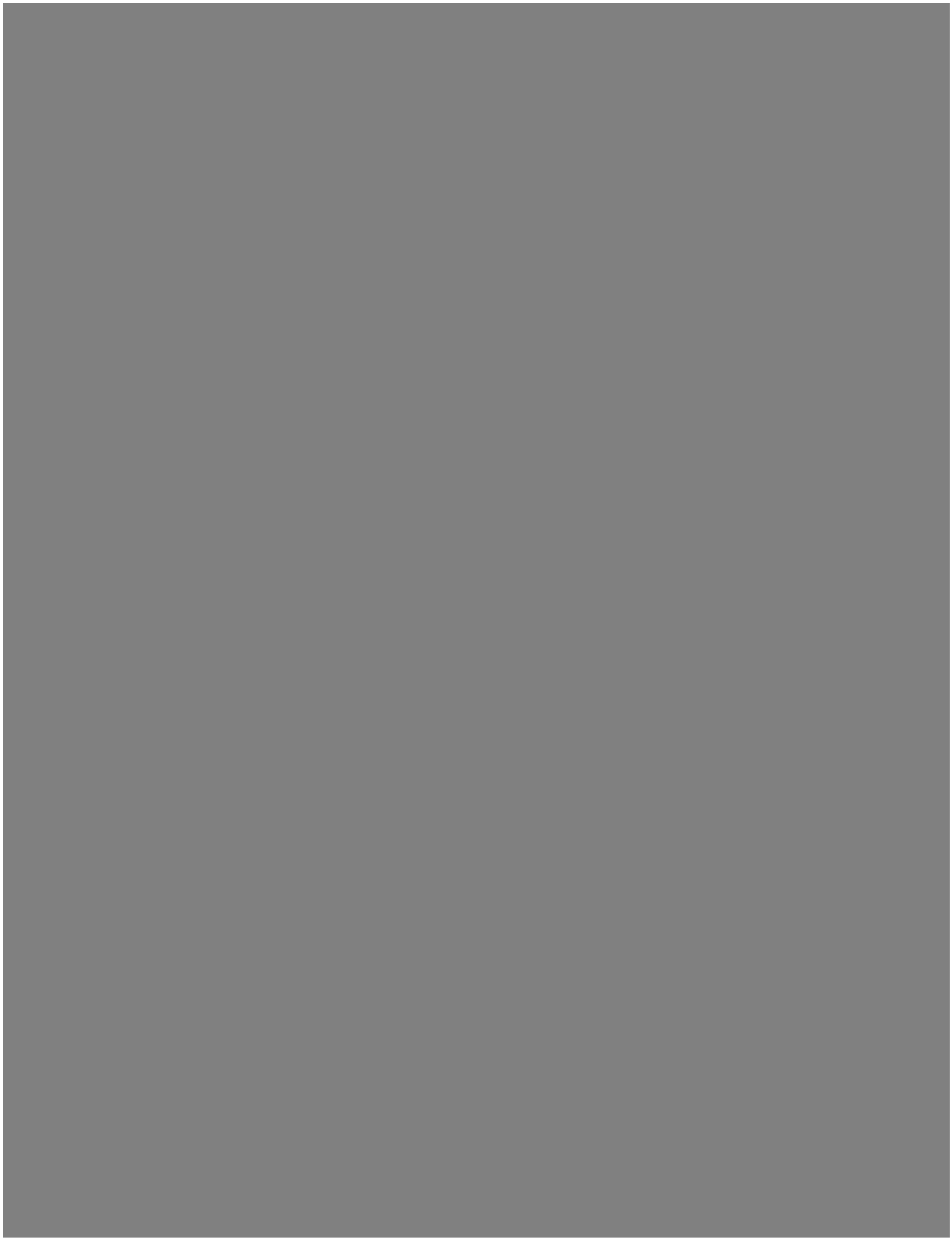
| **Name** | **Role** |
|---|---|
| Dr Charles Ferro | Chief Investigator<br>Consultant Nephrologist and Senior Lecturer, Queen Elizabeth Hospital Birmingham |
| Dr Robert Cramb | Co-investigator<br>Consultant Chemical Pathologist, Director of Pathology Service,<br>Queen Elizabeth Hospital Birmingham |
| Prof Richard McManus | Co-investigator<br>Professor of Primary Care Cardiovascular Research ,<br>Department of Primary Care Health Sciences, University of Oxford |
| Dr Paramjit Gill | Co-investigator<br>Reader in Primary Care Research ,<br>Primary Care Clinical Sciences, University of Birmingham |
| Prof John Townend | Co-investigator<br>Consultant Cardiologist and Senior Lecturer,<br>Cardiology Department, Queen Elizabeth Hospital Birmingham |
| Prof Nick Freemantle | Co-investigator<br>Professor of Clinical Epidemiology & Biostatistics,<br>Primary Care Clinical Sciences, University College London |
| Dr Poorva Jain | Co-investigator<br>Renal Medicine Research Fellow/Registrar in Nephrology,<br>Primary Care Clinical Science, University of Birmingham |
| Dr Khai Ping Ng | Research Fellow<br>Renal Medicine Registrar , Queen Elizabeth Hospital Birmingham |
| Dr Odette Chagoury | Senior Trials Manager<br>Primary Care Clinical Sciences, University of Birmingham |
| Mrs Gurdip Heer | Research Nurse<br>Primary Care Clinical Sciences, University of Birmingham |
| Mrs Val Redman | Trial Coordinator<br>Primary Care Clinical Sciences, University of Birmingham |
| Mr Nick Flint | Lay person |
| Mr Paul Cornick | Lay person |

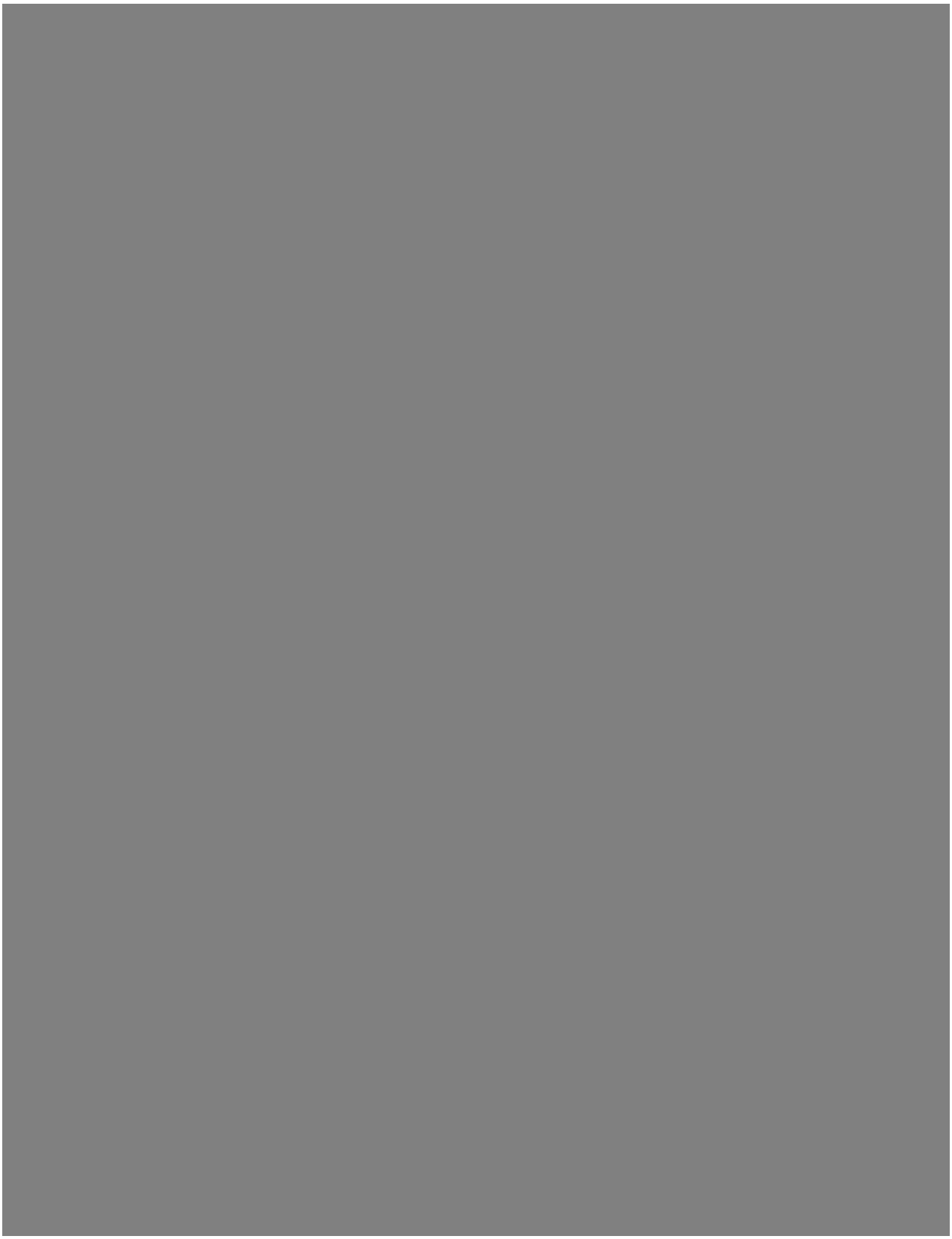
Appendix 4-11: STOP-CKD Data Monitoring Committee Charter

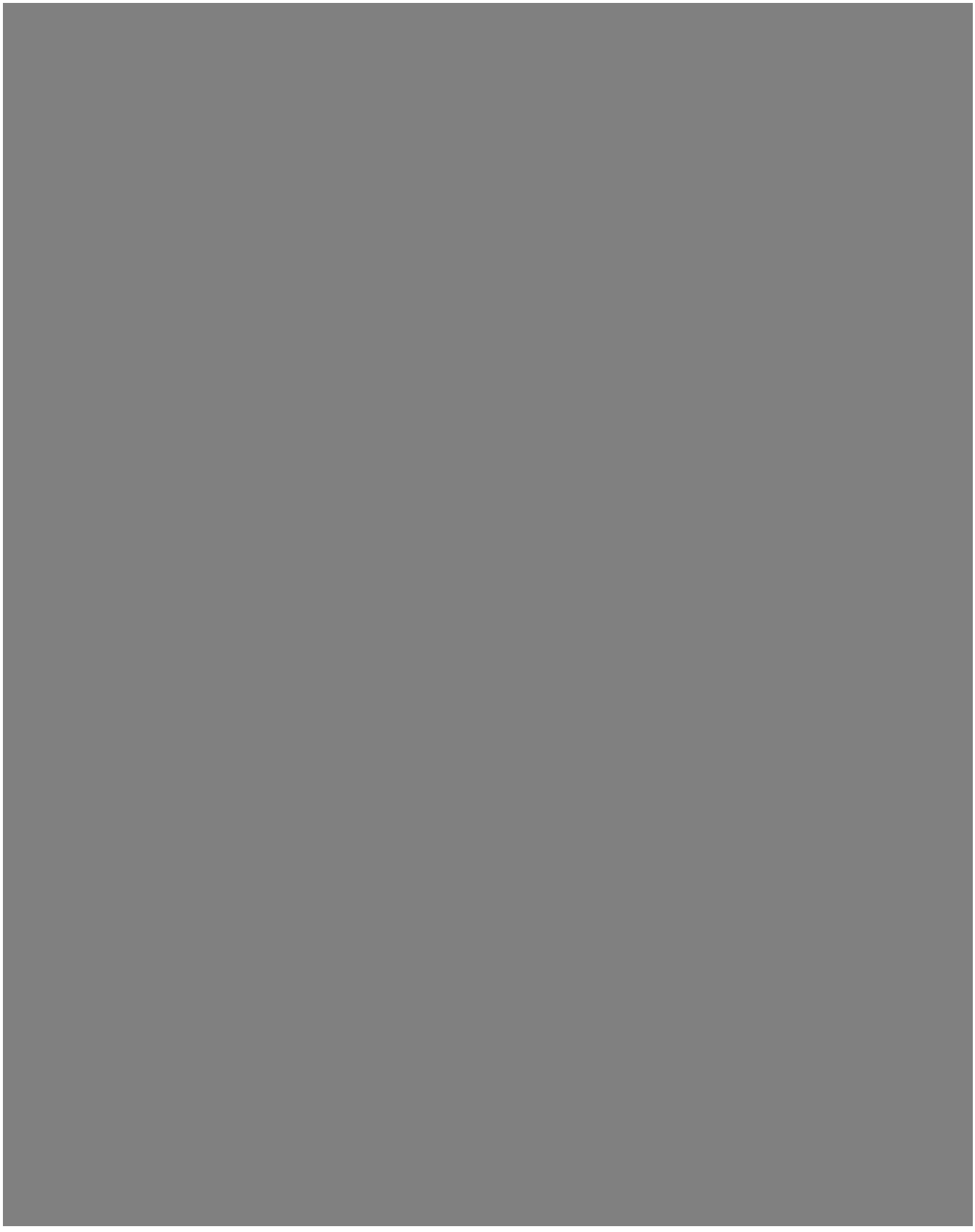












Appendix 6-1: Patient's information sheet for the STOP-CKD interview study

# STOP-CKD

**S**pironolactone **to** **P**revent **C**ardiovascular Events in
Early Stage Chronic **K**idney **D**isease: A Pilot Trial Version 2 24/05/2013

**Interview study**

You are being invited to take part in an interview as part of a research study. Before you decide if you are willing to be interviewed it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends and relatives if you wish. Ask us if there is anything that is not clear or if you would like more information.

**What is the purpose of the interview study?**
This study will explore patients' and general practitioners' views on chronic kidney disease (reduced kidney function), research in chronic kidney disease in the community and the use of a 'water tablet', named spironolactone in patients with chronic kidney disease.

This study will also explore how the barriers to participating in research and the use of spironolactone in patients with reduced kidney function can be addressed.

**Why have I been chosen?**
You have previously indicated your interest in taking part in the interview study.
Our aim is to interview up to 30 patients and 30 general practitioners in this study who have previously decided to take part (or not to).

**What do I have to do?**
We will make an appointment for you at either your local GP practice/healthcare centre or your home. The researcher will then ask you some questions on your views on chronic kidney disease, research in chronic kidney disease and how we can encourage more people to be involved with research studies. The interview will be tape recorded. All information is kept confidential and individuals' details are not given to any other person. The interviews should take no more than 60 minutes. Any travel costs you may incur will be reimbursed.

**Do I have to be interviewed?**
We will telephone you to invite you to take part in an interview. It is up to you to decide whether or not to take part. If you decide to take part we will ask you 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 care you receive.

**What are the possible benefits of taking part?**
Research studies are important in providing useful information for improving healthcare. The information we get from this study may help us in improving our understanding of chronic kidney disease and identifying any potential barriers that may exist to the use of spironolactone. We hope these will facilitate the design of further larger-scale research studies in chronic kidney disease in the community in the future.

**Will my taking part in this study be kept confidential?**

Your name will not be on the tape and we will remove your name from the interview transcripts to keep your identity confidential. Direct quotes may be used in publications but these will be numbered and anything which could identify you will be removed. Nothing that you say will be fed back to the doctors and nurses involved in your care as coming from you.

**Data Protection Act 1998**

The information you give us in the interviews will only be used for the purposes of the study. The information will be kept securely for a period of 5 years after the study ends and then will be destroyed.

**What happens now if I decide to take part?**

If you decide that you would like to participate in this study, we ask you to complete the attached form and send it back to us in the envelope provided. You may also contact us by telephone or e-mail to inform us of your decision to participate.
Dr Khai Ping Ng, STOP-CKD Research Fellow, will then contact you to arrange a convenient day to be interviewed.

**Who is organising and funding the research?**

The National Institute of Health Research is funding the research project, which is being organised by the University of Birmingham.

**Who has reviewed the study?**

Both the National Institute of Health Research and the Research Ethics Committee have reviewed and approved the study.

**Contact for Further Information**

We hope that this leaflet answers some of the questions you may have. If you wish to enquire further about the study, please contact:

Dr Khai Ping Ng (email: KXN262@bham.ac.uk)
Freephone number: **0800 9230329**
STOP-CKD Research Fellow
Primary Care Clinical Research and Trial Unit, University of Birmingham
Edgbaston
Birmingham
B15 2TT

If you are concerned about any aspect of the study and feel the need for independent advice you are recommended to approach your GP or other health professional.

Please return to:

STOP-CKD
Primary Care Clinical Sciences
University of Birmingham
Edgbaston
Birmingham
B15 2TT

Dear Dr Ferro,

Name: ……

Address: ……
……
……
……
……
……

Telephone Number: ……

- ☐ I am interested in participating in this **INTERVIEW** study. I would be happy for a member of the study team to contact me to arrange a date to be interviewed.

- ☐ I do not wish to be involved in this study.

Appendix 6-2: Consent form for the STOP-CKD interview study

| | |
|---|---|
| **Site ID:** | |
| **Patient ID:** | |
| **Patient Initials:** | |

UNIVERSITY OF BIRMINGHAM

# STOP-CKD

**S**pironolactone **to** **P**revent **C**ardiovascular Events in
Early Stage **C**hronic **K**idney **D**isease: A Pilot Trial – Version 2 24/05/2013

## INTERVIEW Study Patient Consent Form

**Please initial each box if you agree with the statement:**

1. I confirm that I have read and understood the STOP-CKD interview study patient information sheet dated 24/05/2013 (version 2). I have had the opportunity to consider the information, to ask questions and have had these answered satisfactorily. ☐
2. I understand that relevant sections of my data collected during the study may be looked at by individuals from the sponsor, regulatory authorities or from the University of Birmingham where it is relevant to my taking part in this research. I give permission for these individuals to have access to my anonymised records. However, I understand that I will not be identified by name in any reports or publications resulting from this study ☐
3. I understand that my participation is voluntary and that I am free to withdraw at any time without giving a reason and without my medical or legal rights being affected. ☐
4. I agree to the interview being recorded and understand that the recordings will be kept safely at the University of Birmingham. ☐
5. I agree that quotes from my interview can be used anonymously in any publication of the research findings. ☐
6. I agree to take part in the above study. ☐

| | | |
|---|---|---|
| ..... | ..... | ..... |
| Name of participant | Date | Signature |
| ..... | ..... | ..... |
| Name of person taking consent | Date | Signature |
| ..... | ..... | ..... |
| Name of Researcher | Date | Signature |

Appendix 6-3: Topic guide for the STOP-CKD interview study

**Patients Interview Topic Prompts**

| | |
|---|---|
| Interview Informed consent obtained? | |

**Opening**

My name is …… I am a researcher from the University of Birmingham. Thank you very much for agreeing to take part in this interview study. I would like to ask you some questions on your views on kidney disease as well as research in kidney disease. The information we get from this interview study may help to improve our understanding in people living with kidney disease, which is important in helping us to improve the healthcare provided for people with kidney disease. This study will also help to improve the design of future research studies in kidney disease. The interview should take no longer than an hour. Is that ok with you?

Everything you say will be confidential. We will make sure that you will not be identified from any comments taken from this interview. This interview will be tape recorded. During the interview, I will also be taking notes, this is for two reasons, firstly as a backup in case something goes wrong with the recorder and secondly to act as a prompt for me to follow up on things you may say. I hope you don't find this too distracting. Do you have any question before we start?

**Understanding of Chronic Kidney Disease**

- Could you talk me through how your kidney condition was first diagnosed?
- Has your GP discussed your kidney condition with you?
- (If yes), what did your GP say?
- (If no), what is your understanding of your kidney condition?
- What do think are the location and functions of kidneys?
- What do you think are the effects of reduced kidney function?
- What do you think are the long-term effects/complications of reduced kidney function?
- Is there anything you would like to know about your kidney condition but has not been explained to you?
- Perception of CKD term
- Family reaction to diagnosis

**Experience of Chronic Kidney Disease**

- Does your kidney condition affect your life?
- (If yes,), how does your kidney condition affect your life?
- When did you become aware of it?
- How did you seek help?
- What treatment have you received so far regarding your kidney condition?
- What do you think about the treatment/care you have received regarding your kidney condition?

**Research in Chronic Kidney Disease**

- Do you have any experience in taking part in medical research study?
- (If yes), could you tell me more about the experience?
- When you decided to/ not to take part in the main research study, what influenced your decision?
- Do you have any views about medical research in patients with reduced kidney function?
- (If yes), what are your views?
- What do you think are the advantage(s) of taking part in medical research?
- What do you think are the disadvantage(s) of taking part in medical research?
- What do you think are the barriers of taking part in research study?
- How do you think we can overcome the barriers?
- If we were going to repeat this study in the future, what do you think we could change to encourage more people to take part?
- Elderly population in research invitation

**Ending**

Thank you. I really appreciate the time you took for this interview. Is there anything else you would like to add or is there anything I have missed?

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