Are recommendations for prescribing applied for older people with reduced kidney function in primary care? A mixed methods study to explore and improve implementation.

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Intellectual Property and Publication Statements

The candidate confirms that the work submitted is her own and that appropriate credit has been given where reference has been made to the work of others.

'Dosis facit venenum'

The dose makes the poison

Paracelsus (1493-1541)

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Abstract

Background

Kidney function reduces with age, increasing the risk of harm and hospital admission from medicines. This project aimed to investigate the extent to which recommendations for prescribing drugs are applied for older people with reduced kidney function in primary care, and what needs to change to improve patient safety.

Research design and methods

A pragmatic sequential mixed methods design was used:

1. Cross-sectional case-note review.
2. Scoping literature review.
3. Primary Care Trust (PCT) wide cross-sectional survey of prescribing data.
4. GP interview study using the Theoretical Domains Framework.
5. Expert and stakeholder consensus group study.

Results

For 8 study drugs across a large PCT, a kidney function too low for recommended use was found for 3.5-39.6% in ≥65 year olds, and 24.2-79.5% in ≥85 years. The Cockcroft Gault equation provides a more accurate estimate of kidney function when prescribing for older people; 68.9-95.3% of patient drug events where kidney function was too low would have been missed if an estimated glomerular filtration rate had been used.

GPs expressed a lack of awareness and knowledge about prescribing when kidney function is reduced. Although they monitored kidney function, it was not thought of when prescribing. Not having warnings and prompts at medication review was a particular barrier identified by GPs, and that the British National Formulary information on prescribing in renal impairment information needs to be clarified.

The priorities for intervention and research agreed were to increase awareness of the need to assess kidney function in the prescribing process for older people, and to provide patient and drug specific warnings and prompts at medication review as well as initiation.

Conclusion

Many older people were taking medication that needed altering, or stopping, because of their reduced kidney function. This research has mapped the prevalence of inappropriate prescribing, and explored the behaviour determinants of GP prescribing, in reduced kidney function in primary care, identified what needs to change in practice, policy, and further research required, to improve patient safety.

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List of abbreviations

ACEI	angiotensin converting enzyme inhibitor
ADE	adverse drug event
ADR	adverse drug reaction
AKI	acute kidney injury
ARB	angiotensin-II receptor blocker
AUC	area under the plasma concentration-time curve
AW	actual weight
BCT	behaviour change technique
BCW	Behaviour Change Wheel
BMI	body mass index
BNF	British National Formulary
CASP	Critical Appraisal Skills Programme
CEBM	Centre for Evidence Based Management
CDSS	computerised decision support systems
CG	Cockcroft Gault equation
CI	confidence interval
CKD	chronic kidney disease
CKD-EPI	the Chronic Kidney Disease Epidemiology Collaboration equation
COREQ	Consolidated Criteria for Reporting Qualitative Research
CPD	continuing professional development
CrCl	creatinine clearance
CrCl-CG	creatinine clearance calculated using the Cockcroft Gault equation
^{51}Cr-EDTA	^{51}chromium edetic acid
DRP	drug related problem
DSS	decision support system
DVT	deep vein thrombosis
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
FDA	Food and Drug Administration (United States of America) (FDA)
GIFA	'Italian Group of Pharmacoepidemiology in the Elderly'
GP	General Practitioner
IBW	ideal body weight
KDIGO	Kidney Disease: Improving Global Outcomes Foundation
MDRD	Modification of Diet in Renal Disease (equation for eGFR)
MHRA	Medicines and Healthcare products Regulatory Agency

MRP	medication related problem
MRSA	methicillin-resistant staphylococcus aureus
NHS	National Health Service (UK)
NICE	National Institute for Health and Clinical Excellence
NOAC	new/ novel oral anticoagulant
NPSA	National Patient Safety Agency
NSAID	non-steroidal anti-inflammatory drug
NSF	National Service Framework
OCEBM	Oxford Centre for Evidence-Based Medicine
OR	odds ratios
PCT	Primary Care Trust
RCCT	randomised cluster controlled trial
RCP	Royal College of Physicians
RCT	randomised controlled trial
RKF	reduced kidney function
SIGN	Scottish Intercollegiate Guidelines Network
SPC	summary of product characteristics (drug licence data sheet)
SrCr	serum creatinine
TDF	Theoretical Domains Framework
TPB	Theory of Planned Behaviour
U&Es	urea and electrolytes
UK	United Kingdom
UKMRC	United Kingdom Medical Research Council
USA	United States of America
UTI	urinary tract infection
WHO	World Health Organisation

Kidney function estimation terms and abbreviations

A table of the kidney function estimation abbreviations used throughout the thesis are presented in Table 1. A full explanation of the terms is given in Chapter 1 (1.2.3), but a brief explanation is included in the table below to provide a simple reminder that is easily accessible.

Kidney function estimation terms and abbreviations

Creatinine clearance (CrCl) – historically used for drug and dosing prescribing decisions, and used for the dosing studies of most available drugs.

        CG - Cockcroft Gault equation

        CrCl-CG - creatinine clearance calculated using the CG equation.

        CrCl-CG AW - creatinine clearance calculated using the CG equation and actual body weight in the equation.

        CrCl-CG IBW - creatinine clearance calculated using the CG equation and ideal body weight (or actual if lower) in the equation.

Estimated glomerular filtration rate (eGFR), reported by pathology laboratories across the UK with kidney function blood test results, and used to stage kidney disease, but not designed for prescribing decisions.

        MDRD - eGFR calculated using the Modification of Diet in Renal Disease equation (used by pathology laboratories at the time of this research).

        CKD-EPI - eGFR calculated using the Chronic Kidney Disease Epidemiology Collaboration Equation (a revised version of the MDRD equation and begun to be introduced into primary care in 2016).

Table 1: Summary table of kidney function terms and their abbreviations.

"The pen is mightier than the scalpel in terms of the damage that you can do to a patient by writing the wrong drug and the wrong dose"

Participant C1, renal physician with a national role (2015)

1 Chapter 1: Background

1.1 Introduction

Reducing the risk of medication for older people has been a focus for most of my career as a pharmacist. On the Elderly Care wards at Leeds General Infirmary, I worked on ensuring parameters such as kidney function were assessed in relation to prescribing, as there are changes with aging, and many clinicians did not seem to be aware that doses might need reducing or alternative drugs used. For the last fifteen years I have worked in Bradford primary care. In that time there has been an increased awareness of kidney disease with the introduction of the National Institute for Health and Care Excellence (NICE) guidelines for chronic kidney disease (NICE CG73, 2008; CG182, 2014) and acute kidney injury (NICE CG169, 2013), and a National Service Framework (NSF) for Renal Services (NSF, 2005). However, my professional experience working in GP practices led me to believe that kidney function was still not routinely assessed in relation to prescribing.

Another concern was that the NICE guidelines introduced a different kidney function estimation equation to assess risk to the kidney, presented as the 'estimation of glomerular filtration rate (eGFR)'. This new equation was giving very different results to the Cockcroft Gault equation (Cockcroft and Gault, 1976) I had always used for decisions on drug use and dosing, when used for assessing the kidney function in older people.

When raising the issue with clinicians they would ask whether it was really a problem. An Elderly Care consultant and researcher, unconvinced that there was an issue, suggested that I should do a study in my workplace that could provide the basis for research if required. So, as a pilot study to prove the concept before applying to do a PhD, I undertook a case-note review at the GP practices where I am a practice pharmacist in Bradford. The results of this study are presented in this chapter as it formed the background for the future research, and supported my application to read for a PhD. The case-note review also started me thinking about prescribing behaviour, and how that might be changed to get prescribing recommendations in reduced kidney function (RKF) applied in practice.

1.2 Context

1.2.1 Risk of harm from drugs

Paracelcus (1493-1541) is credited as first recognising that '*no thing is without poison; the dosage makes it either a poison or a remedy.*' The toxic potency of a chemical is ultimately defined by the dose (the amount) that will produce an adverse reaction in a biological system (Hodgson, 2010).

Minimising risk, to ensure medicines use is as safe as possible, is a key aim of prescribing (Barber, 1995), and one of the four guiding principles of medicines optimisation (Royal Pharmaceutical Society, 2013). However, 'An Organisation with a Memory' (Department of Health, 2000) reported that every year thousands of people are reported to have experienced serious adverse events related to medicines. The Audit Commission report 'A Spoonful of Sugar' (2001) suggested that medication errors account for about one-fifth of deaths due to all types of adverse events in hospital and are an increasingly common stimulus to litigation.

Over half a million medication incidents were reported to the National Patient Safety Agency (NPSA) between 2005 and 2010, with 16% involving actual patient harm (Cousins et al, 2012). There are reports of potential harm for all healthcare sectors:

Hospital inpatients: the General Medical Council's EQUIP study has demonstrated a prescribing error rate of almost 9% (Dornan et al, 2009).

Hospital admissions: adverse drug reactions (ADRs) have been found to account for 6.5% of all hospital admissions (Pirmohamed et al, 2004), with over half judged to be preventable (Howard et al, 2007).

Primary care: an estimated 1.7 million serious prescribing errors occurred in 2010 (Avery et al, 2012).Two recent studies found 13.9% of vulnerable patients were prescribed one or more high risk drugs (Guthrie et al, 2011), and Stocks et al (2015) found the prevalence, of different types of potentially hazardous prescribing, varied between practices from almost zero to 10.2%.

Care homes: over two thirds of residents were exposed to one or more medication errors (Barber et al, 2009).

Adverse drug reactions result in high costs for the healthcare systems, as well as for patients. A systematic review (Wiffen et al, 2002) estimated the overall ADR impact on England to be 4 out of 100 hospital bed-days at a cost of about £380 million a year to the NHS in England. Factors associated with increased incidence of ADR were increasing age, especially over 70 years, increasing number of medicines, and

particular classes of medicine. Non-steroidal anti-inflammatories (NSAIDs) were found to be responsible for between 60% and 70% of all ADRs leading to hospital admission, or causing ADRs within a hospital episode. A recent report commissioned by the Department of Health, 'Exploring the costs of unsafe care in the NHS', showed that hospital admissions for ADRs, and harm related to medicine given during inpatient stays, cost £770 million in 2007, and that £5m was spent on litigation for drug-related medical errors between 1995 and 2007 (Frontier Economics, 2014).

Elimination of drugs via the kidney is a process where there is the potential for patient harm if the kidneys are not functioning normally. Hydrophilic drugs and metabolites are removed from the body more slowly when kidney function is reduced and blood levels rise, increasing the risk of harm (Ashley, 2008). The importance of following recommendations for medicines use in RKF is illustrated by the 'new oral anti-coagulant' (NOAC), dabigatran, where the documented lower dose schedule in renal impairment was not followed leading to a number of cases of serious and fatal haemorrhage reported in elderly patients in Japan (MHRA, 2011).

1.2.2 Drug elimination and reduced kidney function

Elimination from the body of hydrophilic drugs and metabolites via the kidney is by glomerular filtration, renal tubular secretion, and resorption (Matzke and Frye, 1997). Where kidney function is impaired, reduced glomerular filtration and tubular secretion results in higher plasma levels of the drug, and the reduction in resorption causes a higher concentration of drug in the urine. The extent to which drugs are affected depends on the percentage of active drug and/or metabolites that would normally be excreted by the kidney (Ashley and Morlidge, 2008). The Renal Drug Handbook 3rd Edition (Ashley and Currie (Eds), 2009) states that the use of drugs in patients with RKF can give rise to other problems for several reasons:

- Altered pharmacokinetics of some drugs that are variable and complex.
- For many drugs, some or all altered pharmacokinetic parameters are not known.
- Sensitivity to some drugs is increased.
- Many side-effects are particularly poorly tolerated by renally impaired patients.
- Some drugs are ineffective when kidney function is reduced.
- Kidney function generally declines with age.

There are recommendations for use of drugs in RKF in the 'Summaries of Product Characteristics' (SPCs), the Medicines and Healthcare products Regulatory Agency (MHRA) approved and regulated prescribing information for licensed medicines. The

SPC also has a 'pharmacokinetics' section which may give more detail on the elimination of the drug. An example of the effect of kidney function on blood levels is shown in the pharmacokinetic section of the SPC for enalapril which states that "*at a creatinine clearance of <30ml/min the 'AUC'* [area under the plasma concentration-time curve] *is 8 times that at normal kidney function*". AUC is an indicator of the amount of drug that reaches the body over time. Giving a dose of 5mg daily to a person with a kidney function <30ml/min would be giving the equivalent of 8 times the dose i.e. 40mg/day.

The reduction in kidney function affects the pharmacological effects of many drugs, including those of toxic or active metabolites that are excreted by the kidney.

1.2.3 Assessment of kidney function

Kidney function needs to be assessed to inform prescribing decisions, as well as to give a marker of kidney disease and an indication of risk to the kidney. Assessment involves a measurement of glomerular filtration rate which is estimated from the clearance of a solute present in a stable concentration in the plasma and freely filtered by the kidney. A naturally occurring solute used is creatinine, a product of muscle breakdown, which is currently the one used in practice (Ashley and Morlidge, 2008). Twenty-four hour urine collection gives a direct measurement of the clearance of creatinine, but is not usually practical. Kidney function is normally estimated using the serum creatinine level and a calculation using a standard equation, which introduces limitations; for example the terms for age, sex, and race only capture some of the determinants of creatinine concentration in blood plasma, and the coefficients represent average effects observed in the population used to develop the equations. The kidney function estimation equations, and their limitations, are discussed in more detail in the following sections (1.2.3.1, 1.2.3.2). Table 2 provides a summary of the equations with the abbreviations used throughout the thesis. This table is reproduced at the end of the abbreviations list (Page 22, Table 1) to provide an easily accessible reference.

Up until the first CKD UK guidelines were introduced in 2005 (Joint Specialty Committee for Renal disease of the Royal College of Physicians of London and the Renal Association, 2005), the most widely used equation to estimate kidney function was the Cockcroft Gault equation (Cockcroft and Gault, 1976). However, the new guidelines introduced the use of 'estimated glomerular filtration rate' (eGFR) calculated using the Modification of Diet in Renal Disease (MDRD) equation (Levey et al, 1999), and in the recently updated NICE guidelines (NICE CG182, 2014) the 'Chronic Kidney

Disease Epidemiology Collaboration' (CKD-EPI) equation has been introduced to estimate glomerular filtration rate of creatinine.

Kidney function estimation terms and abbreviations

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Estimated glomerular filtration rate (eGFR), reported by pathology laboratories across the UK with kidney function blood test results, and used to stage kidney disease, but not designed for prescribing decisions.

    MDRD - eGFR calculated using the Modification of Diet in Renal Disease equation (used by pathology laboratories at the time of this research).

    CKD-EPI - eGFR calculated using the Chronic Kidney Disease Epidemiology Collaboration Equation (a revised version of the MDRD equation and begun to be introduced into primary care in 2016).

Table 2: Summary table of kidney function terms and their abbreviations (reproduced on Page 22 with the abbreviations table).

Recent publications on use of the 'new oral anticoagulants' (NOACs) have illustrated the difficulty of applying the recommendations for use in RKF because of the different equations used for estimating kidney function, concluding that CrCl calculated using Cockcroft Gault should be used to reduce the risk of overdose and bleeding, and not eGFR (Heidbuchel et al, 2013; Wood et al, 2013).

The complexity and limitations with using the kidney function estimation equations is initially explored in the following sections. The uncertainty in using each equation this engenders suggested the need for a scoping review of the available evidence for

assessing kidney function when prescribing for older people, and is explored in more depth in the literature review (Chapter 2, 2.6).

1.2.3.1 Creatinine clearance (CrCl)

CrCl calculated using the Cockcroft Gault equation

Creatinine clearance is the originally used estimate of kidney function, calculated by the Cockcroft Gault equation (Cockcroft and Gault, 1976). It has been used historically in drug company dosing studies and the SPCs quote recommendations for dosing in renal impairment as CrCl. The BNF states that '*published information on the effects of renal impairment on drug elimination is usually stated in terms of creatinine clearance'*. Some SPCs emphasise the need to use the Cockcroft Gault equation by writing it out in full, for example for gabapentin, pregabalin and edoxaban. The Cockcroft Gault equation is shown in Figure 1. Where creatinine clearance has been estimated using the Cockcroft Gault equation, rather than, for example, directly measured, the abbreviation 'CrCl-CG' has been used throughout the thesis.

The Cockcroft Gault equation (Cockcroft and Gault, 1976)

Creatinine clearance (CrCl-CG) ml/min = $\dfrac{F \times (140 - \text{age}) \times \text{IBW (kg)}}{\text{Serum creatinine (micromol/l)}}$

Where F = 1.23 for males or 1.04 for females

IBW = ideal body weight (or actual body weight if lower)).

Figure 1: The Cockcroft Gault equation for kidney function estimation.

Limitations

The Cockcroft Gault equation has been criticised as it was developed using only a small sample of Caucasian men (Cockcroft and Gault, 1976) and so would have limitations in being generalised to other populations such as women, older people, and different ethnic groups. Helou (2010) comments that the success of the Cockcroft Gault equation is not due to the original study, but to its validation in several later studies for different populations, including for older people, compared to both measured CrCl values and reference glomerular filtration rate measurement methods,.

The Cockcroft Gault equation includes a weight factor. Creatinine is formed from muscle turnover and so the weight element needs to give an indication of muscle mass, and not excess body fat; for this reason, ideal body weight (IBW) is

recommended in the British National Formulary (BNF70, 2015). The need for a weight to calculate CrCl-CG was suggested to reduce the feasibility of reporting in primary care. Patients may not have a weight on the record, and pathology laboratories would not have access to a patient's weight to be able to report CrCl-CG with kidney function monitoring results.

Primary care patient record systems do not all have a calculator to help prescribers calculate CrCl-CG. Even where there is a calculator, such as on the 'SystmOne' 'renal calculator', the prescriber would need to know where to find it and when to use it as there are no prompts or sign-posts to its use.

Hellou's review (2010) found that, although there were major limitations in the original Cockcroft Gault equation development study, later studies have validated its use, including for older people. Hudson & Nyman (2011) state that, as dosing regimens for most currently available drugs are based on pharmacokinetic studies that have used CrCl-CG as the measure of kidney function, it is the most appropriate estimate to use when making prescribing decisions.

1.2.3.2 Estimated glomerular filtration rate (eGFR)

a) eGFR calculated using the MDRD

In 2008 the NICE guidelines for chronic kidney disease (CKD) (NICE CG73, 2008) established the term 'estimated glomerular filtration rate' (eGFR) calculated using the 4 variable MDRD equation (Figure 2). The guidelines recommend use of MDRD as this equation does not require a value for patient weight and can therefore be easily calculated using clinical laboratory instrument software. The eGFR is now reported by pathology laboratories across the UK with kidney function blood test results, and is used to stage kidney disease.

The Modification of Diet in Renal Disease equation (Levey et al, 1999)

eGFR ml/min/1.73m^2 = 175 x [serum creatinine (micromol/l)]$^{-1.154}$ x age (years)$^{-0.203}$

$$88.4$$

x 0.742 if female

x 1.21 if African American or African Caribbean

Figure 2: The MDRD equation for kidney function estimation.

Limitations

The MDRD equation was not designed to give a kidney function estimation for drug dosing decisions. It was developed to give an indication of risk to the kidney and allow staging of kidney function to guide monitoring and treatment of CKD. For drug prescribing it is not important whether the reduced kidney function is a factor of senescence, kidney disease or acute kidney injury. Section 1.2.4 discusses further the effect of old age on kidney function and that a reduced kidney function is not necessarily as a result of disease. Even for assessment of kidney disease, the validation studies for eGFR did not include people aged over 65 years (Spruill, 2008).

Across the UK eGFR is now reported from pathology laboratories with all kidney function blood tests (urea and electrolytes (U&Es) including serum creatinine) making it readily available on the patient record to give an indication of kidney function level. One problem with its use highlighted by the 'Kidney Disease: Improving Global Outcomes Foundation' (KDIGO) is that the eGFR is reported per body surface area (BSA) of $1.73m^2$ but the figure is never adjusted in practice for individuals where BSA is different, which could lead to error. For example, a male patient with a BSA of $2.28m^2$ has a larger body surface area and so should have the eGFR adjusted: a reported eGFR of 70 ml/min/$1.73m^2$ should be adjusted for the BSA to 53.1 ml/min. A threshold for CKD is 60 ml/min and whether the BSA had been accounted for or not would alter the assessed stage of kidney disease for this patient, and the consequent management.

Since 2010, the British National Formulary (from BNF59, 2010) has quoted renal impairment recommendations as 'eGFR' but the figures are taken from the drug SPCs, where exactly the same figures are CrCl-CG. The BNF states that, although CrCl and eGFR are not interchangeable, for most patients the eGFR is an adequate approximation of CrCl, but that calculation with the Cockcroft Gault equation should be used for '*potentially toxic drugs with a small safety margin*', and the Cockcroft Gault equation is provided in the 'Prescribing in Renal Impairment' section.

As the abbreviation 'eGFR' is used widely where the calculation has been with the MDRD equation, eGFR will be used in the rest of this thesis to mean estimated glomerular filtration rate calculated using the MDRD equation (see Summary Table 1 and 2).

b) eGFR calculated using the Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPI)

The most recent NICE guidance for chronic kidney disease (NICE CG182, 2014) has introduced the change that clinical laboratories should use the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation to estimate the glomerular filtration rate of creatinine (Figure 3).

CKD-EPI is based on the same four variables as the MDRD Study equation, but uses a different model for the relationship between estimated glomerular filtration rate and serum creatinine, and an altered relationship for age, sex and race. It has been reported to 'perform better', and with less bias, than the MDRD Study equation, especially in patients with higher glomerular filtration rate, which results in reduced misclassification of CKD (Levey et al, 2009).

The Chronic Kidney Disease Epidemiology Collaboration equation (Levey et al, 2009)

eGFR ml/min/1.73m^2 = 141 × min (Scr /κ, 1)α × max(Scr /κ, 1)-1.209 × 0.993Age × 1.018 [if female] × 1.159 [if black]

where:Scr is serum creatinine in mg/dL,

κ is 0.7 for females and 0.9 for males,

α is -0.329 for females and -0.411 for males,

min indicates the minimum of Scr /κ or 1, and

max indicates the maximum of Scr /κ or 1.

Figure 3: The CKD-EPI equation for kidney function estimation

Limitations

CKD-EPI has similar limitations to MDRD in relation to use for drug prescribing decisions. It has been developed, and declared to 'perform better', for classification of kidney disease and assessment of risk to the kidney, not for prescribing decisions. It does not have a weight element to the equation, and is also reported as ml/min/1.73m^2 so it is also unlikely to be adjusted to body surface area. Like MDRD, the validation studies did not assess performance for older people.

Since the recent change in NICE recommendation (NICE CG182, 2014), reporting of eGFR using CKD-EPI is not yet widespread in routine use. For the duration of this research MDRD was the equation used by pathology laboratories, and in this thesis

the abbreviation 'eGFR' will mean that the MDRD equation has been used (see Summary Table 1 and 2).

1.2.4   Kidney function and prescribing for older people

1.2.4.1   Kidney function reduces with age

Glomerular filtration rate slowly decreases with aging as a normal biological phenomenon linked to cellular and organ senescence (Beers and Berkaw, 2000; Grimley-Evans et al, 2000; Glassock and Winearis, 2009). On average the decline has been found to be approximately 0.9-1ml/min annually after the age of 30 years, and decreases more rapidly after 65 years (Lindeman et al, 1985). Confounding factors such as hypertension, coronary heart disease, congestive heart failure, the use of nephrotoxic drugs, and super-imposed kidney disease contribute to the rate and magnitude of the kidney function decline (Ponticelli et al, 2015). The Renal Drug Handbook states that many older people have a glomerular filtration rate of <50ml/min which because of reduced muscle mass, may not be reflected by an elevated creatinine. Both muscle mass and creatinine turnover reduce at a similar rate with increasing age leading to serum creatinine levels tending to remain normal and not reflecting a decline in kidney function for older people (Ashley and Currie, 2014). Although they state that 'mild renal impairment can be assumed for the elderly', the complexity of natural decline, and the effects of disease and drugs, means that an assessment of kidney function needs to be made in order to make decisions on doses of drugs excreted by the kidney (Ashley and Morlidge, 2008).

Glassock and Winearis (2009) argue that the 'new paradigm' introduced in the last 15 years of 'eGFR' calculated using the MDRD equation is unadjusted for the effects of age. The combination of eGFR and the introduction of the new classification for diagnosis and staging of CKD used in the NICE guideline (National Kidney Foundation, 2002) has led to the unintended consequence of misclassification of many older people, often females, as having CKD when they are within a normal range for their age. The fact that the MDRD equation is unadjusted for the effects of age would also affect assessment of the level of kidney function for drug prescribing decisions, irrespective of whether it is a factor of senescence or disease.

1.2.4.2   Risk of harm for older people

Older people are therefore more at risk from drugs that are affected by renal impairment because of a naturally reduced kidney function as age increases. The effects of chronic conditions can have an added effect. Older people are more likely to be taking regular medications, with around 75% of those aged 60 years and older, and

over 90% in the over 70s taking at least one prescribed medicine (Petty et al, 2014). The mean number of medicines per patient on repeat prescriptions is over 5 for the 60-69 year olds, and up to 7.1 for the over 80s (Petty et al, 2014). The Health and Social Care Information Centre (2014) reported that about 600 million (60 per cent) of the one billion drug items dispensed in the community in 2013 were for people aged 65 years or over. As discussed in section 1.2.1., factors associated with increased incidence of adverse drug reactions were increasing age, especially over 70 years, and increasing number of medicines (Wiffen et al, 2002). Helldén et al (2009) found that 14% of hospital admissions of elderly patients in Sweden were primarily caused by ADRs and one-third were related to impaired kidney function.

1.2.4.3   Kidney function within the context of other age-related functional decline

With ageing, there is a progressive loss of the functional capabilities of most body organs, changes in responses to receptor stimulation and a decrease in homeostatic mechanisms, which have implications for drug handling. Of these changes, excretion is the most significant and important age-related pharmacokinetic change and is both predictable and measurable. Two-thirds of people aged 70-80 years having approximately half the kidney function of a young adult (Beers and Berkow, 2000; Grimley-Evans et al, 2000).

Other pharmacokinetic changes also impact on the body's handling of drugs. The liver reduces in size and blood flow declines, but overall metabolism of drugs tend to be only slightly impaired in the absence of liver disease. Drugs with a high first pass metabolism, such as morphine, will have higher blood levels where blood flow to the liver is reduced. However, liver function is not easily measurable; liver function tests indicate liver damage, but not metabolic effectiveness. Also, the clinical significance varies widely between individuals. Abnormal liver function tests can indicate the need for caution when prescribing drugs that are metabolised, but not specific levels that determine effect (Beers and Berkow, 2000; Grimley-Evans et al, 2000).

Absorption of drugs is largely unchanged with ageing, but changes in body composition can mean water soluble drugs such as digoxin have a reduced volume of distribution and so higher blood levels needing reduced initial doses. Lipid-soluble drugs such as diazepam are concentrated in the larger volume of body fat and the half-life increases. There may be significant reductions in serum proteins in extreme old age, and in disease, that may affect highly protein bound drugs such as phenytoin. These effects are not easily measurable, and so the recommendations are for caution

and reduced dosing for older people (Beers and Berkow, 2000; Grimley-Evans et al, 2000).

Individuals vary widely as to whether, and to what extent, changes in receptor effect (pharmacodynamics) and homeostatic changes, would affect prescribing. For example cardiovascular changes such as a reduced orthostatic circulatory response leading to postural or orthostatic hypotension and falls. Drugs can add to this effect and exacerbate increased blood levels, for example where kidney function is reduced (Beers and Berkow, 2000; Grimley-Evans et al, 2000).

The endocrine system and particular endocrine organs, including the thyroid, undergo functional changes during aging (Gesing et al, 2012). The prevalence of thyroid disorders increases with age but symptoms are more subtle and are often attributed to normal aging. As changes occur with increasing age, the need for regular monitoring is important to reduce the risk of harm from drugs.

1.2.4.4   Increasing population of older people

The impact for older patients, and the NHS, will be more significant in the future with changing population demographics. There will be 5½ million more people aged ≥65 years by 2030 in the UK, and 19 million by 2050. People ≥80 years will almost double by 2030 reaching 8 million by 2050 (Cracknell, 2010).

1.2.4.5   Research and older people

Avorn (2010) highlights the problem that patients older than 65 years (and especially over 80 years) remain under-represented in clinical trials despite benefitting at least as much, and that costs of illnesses prevented or caused by pharmacotherapy are far greater than drug costs alone.

As discussed in 1.2.3, the MDRD and CKD-EPI kidney function estimation equations were not designed for drug dosing decisions and the development studies did not evaluate performance for older people. However, eGFR is the estimate reported by pathology laboratories. People aged 65 years and older took 60% of all dispensed medications in England & Wales in 2013 (Health and Social Care Information Centre, 2014) emphasising the importance of including older people in the development and assessment of these equations, and for research focussed on this age group.

The widespread use of medications by older people, the increased risk because of a reduced kidney function, and the complexity and confusion arising from the introduction of eGFR, suggested that a pilot study should be conducted to assess whether research was required.

1.3 Are recommendations for prescribing in reduced kidney function applied in GP practice?

Kidney function reduces with age which affects many drugs, but experience as a pharmacist in primary care suggested that this was not accounted for when prescribing for older people. Slower elimination of drugs could mean increased blood levels and risk of harm. As there had been some scepticism about whether this was really the case in primary care, it was suggested that a pilot study was undertaken as a proof of concept before applying to study for a PhD. A cross-sectional GP practice based case-note review was therefore undertaken which aimed to investigate whether recommendations for prescribing in RKF were being applied (Wood et al, 2011).

1.3.1 Objectives

The objectives were to assess:

- The prevalence of patients aged 65 years and older with a documented eGFR<60ml/min/1.73m^2 (NICE CG73, 2008) on drugs not recommended to be prescribed, or which need an altered dose, using the Cockcroft Gault equation to calculate creatinine clearance (CrCl-CG).

- Which drugs were prescribed outside the recommended use in this population.

- Whether using eGFR or CrCl-CG kidney function estimates would alter dosing decisions.

- Whether there was any record of harm caused by use of drugs outside the recommendations in RKF.

1.3.2 Study design

1.3.2.1 Setting

The study was run in 5 GP practices in North Bradford. Each practice had a team of GPs and had list sizes ranging from 4,993 to 11,926 in the same urban area of Bradford. Practices A and B were my main places of work and I had done audits and run workshops on use of drugs in RKF. Practices C, D and E also had practice pharmacist input and some audit work including checking kidney function for use of drugs.

1.3.2.2 Participants

The study reviewed the clinical record of people registered at the 5 GP practices aged 65 years or older whose latest kidney function test result recorded was reduced

(eGFR<60ml/min/1.73m^2), as defined by the NICE chronic kidney disease guideline (NICE CG73, 2008).

1.3.2.3 Sample

All patient records at Practice A aged 65 years and over with the most recent documented eGFR <60ml/min/1.73m^2 were reviewed. At practices B, C, D and E, a 10% random sample of all patients aged 65 years and over with an eGFR <60 ml/min/1.73m^2 were reviewed, using a random number generator (Stattrek, 2010).

1.3.2.4 Method

Case-note reviews were performed between March and June 2010. For each review:

- The eGFR was recorded from the patient record and CrCl-CG calculated.

- All drugs on the repeat medication list were reviewed for appropriateness of drug use and dosing, assessed against recommendations given in the British National Formulary (BNF, 2010) and the Summary of Product Characteristics (SPC).

- Although the study was not set up to systematically assess rates of adverse drug reactions (ADRs), if any were found relating to the use of medications in RKF, they were noted.

- Action required was followed up with the prescriber.

1.3.2.5 Data collection

A data collection form was developed and completed for each review done, to systematically capture the required data (Appendix 1, 8).

1.3.2.6 Analysis

A quantitative descriptive analysis was performed.

1.3.2.7 Governance approval

Approval was given as a service evaluation by the Primary Care Trust (PCT) governance lead, and participating practices, as part of the existing prescribing support service. NHS ethical approval was not required as it was an in-house service evaluation. Patient identifiable data was kept at the practice at all times, results were fed back to practices, and high risk cases followed up.

practice	total practice poulation	number aged 65yrs or older		number aged ≥65yrs and eGFR<60		records reviewed of patients aged ≥65yrs and eGFR<60		people aged ≥65yrs and eGFR<60 reviewed								number of drug items needing stopping or dose reducing	number of drug items needing stopping, dose reducing or review
								number with eGFR<30		number with CrCl<30		number on a drug needing to be stopped or dose reduced		number on a drug needing to be stopped, dose reduced or review			
		n	%	n	%	n	%	n	%	n	%	n	%	n	%		
A	8,993	1,285	14.3	406	4.5	406	100	29	7.1	118	29.0	88	21.7	96	23.6	123	189
B	11,926	2,019	16.9	706	5.9	71	10	5	7.0	19	26.8	13	18.3	17	23.9	21	29
C	11,446	2,164	18.9	510	4.5	51	10	3	5.9	15	29.4	14	27.5	16	31.4	24	35
D	10,883	1,673	15.4	411	3.8	41	10	2	4.8	14	34.1	14	34.1	14	34.1	22	37
E	4,993	803	16.1	246	4.9	25	10	2	8.0	7	28.0	6	24.0	8	32.0	11	18
Total	48,241	7,944	16.5	2,279	4.7	594	26	41	6.9	173	29.1	135	22.7	151	25.4	201	308

Abbreviations: eGFR: estimated glomerular filtration rate; CrCl: creatinine clearance

Table 3: Summary of the case-note review results from 5 GP practice

1.3.3 Results

Highlighted figures in the tables are those mentioned in the text, results or discussion.

1.3.3.1 Prevalence of inappropriate drug use for older people with RKF

Drugs needed to be stopped, or the dose reduced, for 22.7% (n=135) of the 594 patients reviewed aged 65 years or older with an eGFR<60ml/min/1.73m^2 (practice range 18.3%-34.1%), using CrCl-CG to determine the suitability of drug and dose. The results obtained from the five practices are summarised in Table 3. If drugs needed review because of a low kidney function are included then the prevalence was 25.4% (n=151) (range: 23.6%-34.1%).

In practices A and B the proportion of people on drugs that needed stopping, dose reducing or review were 23.6% and 23.9% respectively (Table 3). For practices C, D, and E it was 31.4%, 34.1%, and 32.0% respectively.

A total of 201 drugs listed as repeat medication on the 594 patient records reviewed needed stopping or the dose reducing, and a further 107 drugs needed review (total = 308).

1.3.3.2 Drugs implicated

Seventy different types of drug were found to be used sub-optimally in this group of patients, listed in Table 4, and in more detail in Appendix 2 (8.2).

The groups of drugs most frequently encountered in the audit are illustrated in Figure 4 with lipid-lowering drugs the highest (30%), followed by angiotensin converting enzyme inhibitors (ACEIs) and angiotensin-II receptor blockers (ARBs) (26%), thiazides (17%), and osteoporosis drugs (14%).

1.3.3.3 Categories of inappropriate drug use in RKF

Four categories of inappropriate drug use were identified from this case-note review (Table 4):

Avoid: 23% were drugs that are recommended to be avoided at levels of kidney function below a specified level, including alendronic acid, rosuvastatin and metformin.

Reduce dose: 28% were drugs that are recommended to have the dose reduced at levels of kidney function below a specified level, including simvastatin, allopurinol and gabapentin.

Ineffective: 16% were drugs that are ineffective at levels of kidney function below a specified level, including thiazides and nitrofurantoin.

Caution: 33% were drugs where the guidance is unspecific caution but are known to cause ADRs in RKF, including NSAIDs, ACEIs and ARBs.

to be avoided in low kidney function		dose to be reduced in low kidney function		ineffective in low kidney function		use with caution in low kidney function	
drug	n	drug	n	drug	n	drug	n
alendronic acid	24	simvastatin	52	bendroflumethiazide	24	ramipril	18
metformin	13	allopurinol 300mg	8	indapamide	5	frusemide	13
Calcichew D3 forte	10	atenolol 100mg	7	chlortalidone	5	candesartan	10
rosuvastatin	8	ranitidine	5	hydrochlorthiazide	1	valsartan	10
lercanidipine	5	digoxin	3	nitrofurantoin	1	lisinopril	9
moxonidine	2	baclofen	2	Zestoretic	1	codeine 30mg	5
strontium	2	atenolol 50mg	1			ibuprofen gel	4
anastrazole	1	bezafibrate	1			calcium no vit D	3
eplenerone	1	ciprofibrate	1			irbesartan	3
ibandronic acid	1	colchicine	1			spironolactone	3
risedronate	1	domperidone	1			lamotrogine	3
sitagliptin	1	fenofibrate	1			losartan	3
sulfasalazine	1	gabapentin	1			escitalopram	2
metoclopramide	1	hydroxyzine	1			ibuprofen	2
minocycline	1	venlafaxine	1			diclofenac gel	2
		amylobarbital	1			diclofenac	2
		mirtazapine	1			perindopril	2
		pantoprazole	1			prochlorperazine	2
		tramadol	1			telmisartan	2
						bumetanide	1
						buprenorphine patch	1
						citalopram	1
						enalapril	1
						felbinac gel	1
						fosinopril	1
						olmesartan	1
						primidone	1
						propranolol	1
						quinapril	1
						sertraline	1

Table 4: The 70 different types of drugs judged to be used inappropriately in RKF with n = number found to need altering or review in 594 record reviews (from Appendix 2).

1.3.3.4 Kidney function estimation equations

Figure 5 shows that 29.1% of patients aged ≥65 years with a documented eGFR <60ml/min/1.73m^2 were calculated to have a CrCl-CG of <30ml/min whilst 6.9% had an eGFR <30ml/min/1.73m^2.

For 22.2% (n=132) the equation used would result in a different decision being made about whether a drug could be safely used or whether a dose needed altering.
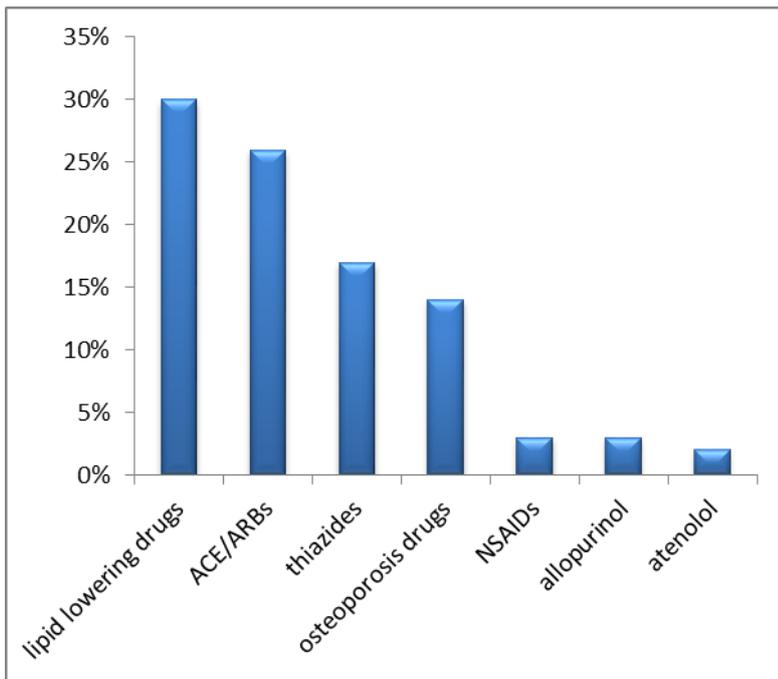
Abbreviations: ACE: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker; NSAID; non-steroidal anti-inflammatory.

Figure 4: The most frequently encountered drug classes not used as recommended in RKF in the case-note review.
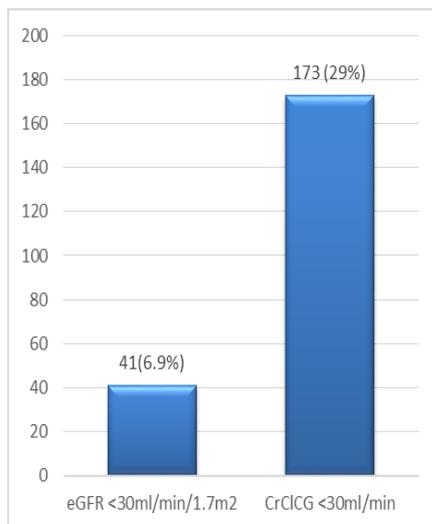
Abbreviations: eGFR: estimated glomerular filtration rate; CrCl-CG: creatinine clearance Cockcroft Gault

Figure 5: The number of patients with an eGFR < 30ml/min/1.7m² and CrCl-CG <30ml/min.

1.3.3.5 Record of harm caused

The study was not set up to systematically assess rates of ADRs so overall rates of harm were not possible to asess. However, whilst reviewing the case notes, four examples of ADRs were recognised to be caused by drugs used in RKF and are described:

Anaemia on sulfasalazine

- A 78 year old lady had an eGFR recorded as 25 ml/min/1.73m^2 six months previously and was taking sulfasalazine 2.5g/day. The lady had been investigated for anaemia and had blood transfusions but was still on the high dose of sulfasalazine. The CrC-CGI was calculated as 16ml/min. The SPC states that levels of sulfasalazine over 50mcg/ml are associated with a substantial risk of ADRs. The renal clearance constant is 125 ml/min corresponding to the glomerular filtration rate so, if the filtration rate is reduced to 16ml/min then the elimination of sulfasalazine would be reduced by approximately eight times and the plasma levels would be much higher making ADRs such as anaemia more likely.

Digoxin toxicity causes hospitalisation

- An 81 year old gentleman had been admitted to hospital in January 2010 with digoxin toxicity after a bout of diarrhoea. His weight was 39kg and CrCl-CG calculated as 23ml/min meaning a low renal reserve.

Acute kidney injury on an angiotensin converting enzyme inhibitor (ACEI) and a diuretic

- An 81 year old lady on ramipril 10mg (maximum recommended dose if CrCl<50ml/min is 5mg) and furosemide 20mg. The serum creatinine had been rising and a 'U&Es' kidney function check had shown an eGFR of 13 ml/min/1.73m^2 and a CrCl-CG of 11ml/min with a much increased potassium level, showing acute kidney injury.

- A 76 year old man with chronic kidney disease, and CrCl-CG calculated as 21ml/min, on lisinopril 20mg, furosemide 80mg and spironolactone 50mg was admitted to hospital with acute kidney injury shown by a very increased serum creatinine and raised potassium level. He was admitted to the renal unit and the ACEI and spironolactone were stopped.

Any high risk cases found that needed action, follow-up or review were highlighted to the relevant prescriber.

1.3.4   Discussion

1.3.4.1   Principal findings

Prevalence of inappropriate drug use in RKF

A quarter of all people reviewed aged 65 years and older with a documented reduced kidney function estimate on their record were found to be taking a drug that should be stopped or the dose reduced. As drug levels are likely to be higher when kidney function is reduced there is an increased risk of harm for these patients.

Practice A and B are both practices that I have worked with for a number of years where I have done audits that have included checking kidney function, for example statin and bisphosphonate switches. I have also run workshops at both practices on prescribing in RKF and use of the readily available resources. At both practices, 24% of patients with a documented RKF were on drugs that needed stopping, dose reducing or review. However, the results from the other three practices showed even higher proportions (31%, 34%, and 32%). My intervention at practices A and B of education, audit and feedback may have had an effect on prescribing in RKF, but there were still a quarter of people reviewed with a documented reduced eGFR who were on drugs or doses that were not within the recommendations.

Drugs found to be used inappropriately in RKF

Seventy different types of drug were used outside recommendations in RKF with 308 instances found for the 594 people reviewed.

Simvastatin was the drug most found to be used inappropriately (52 patients). It has an alternative that can be used at low kidney function (atorvastatin), so it can be avoided and reduce the risks of high plasma levels such as rhabdomyolysis (SPC).

Out of 61 ACEI or ARB prescriptions identified, 8 were inappropriate and the rest were high dose that needed review. As they are partly or mainly excreted by the kidney, reduced levels of kidney function can increase blood levels and, as they can also be nephrotoxic, kidney function can drop further leading to acute kidney injury.

Thiazides were the next most implicated drugs – bendroflumethiazide, chlorthalidone, hydrochlorthiazide and indapamide in 35 patients. Thiazides are ineffective at CrCl <30ml/min (BNF, 2010) and so they will not be having the desired effect for these patients but may be putting the patient at higher risk of side effects such as electrolyte disturbance.

Twenty eight patients were on drugs for osteoporosis that were not as recommended: alendronic acid (24), strontium (2), ibandronic acid (1) and risedronate (1). All have

recommendations to be avoided at specified levels of kidney function. The bisphosphonates are deposited in bone and have a terminal half-life of over 10 years (SPC).

Non-steroidal anti-inflammatories (NSAIDs) can affect all stages of kidney function and are frequently implicated in making kidney function worse (Ashley & Morlidge, 2008). They are highlighted in both the NICE and SIGN guidelines (NICE CG73, 2008; SIGN guideline 103, 2008) as being a risk factor for impairment of kidney function. In the case-note review 10 patients were found with NSAIDs on their repeat medication list, with 6 of these being as a topical formulation (systemic levels will be significantly lower than for oral formulations but the NSAID gels have been implicated in adverse drug reactions). Although the numbers found were low, there is a high risk of ADR and hospital admission. Also, many NSAIDs are prescribed acutely or are bought by patients themselves; these would not have been found in the case-note review, but could be significant if they have a low level of kidney function.

This case-note review has highlighted four categories of inappropriate use in RKF:

- **Drugs that are recommended to be avoided at levels of kidney function below a specified level** (23%). In RKF the drug will be too slowly excreted by the kidney, blood levels of the drug will be raised and the risk of harm increased. An example is alendronic acid which should be avoided at CrCl less than 35ml/min (SPC).

- **Drugs that are recommended to have the dose reduced at levels of kidney function below a specified level** (28%). The dose should be reduced in RKF or blood levels are likely to be increased with a risk of side effects. Simvastatin has a recommendation to not use doses above 10mg if the CrCl is <30ml/min (SPC).

- **Drugs that are ineffective at levels of kidney function below a specified level** (16%). Not only could harm be caused from ineffective treatment, but side effects are more likely. Nitrofurantoin is not likely to work at CrCl lower than 45ml/min (MHRA, 2014) but there is a significant association between RKF (<50 ml/min/1.73 m²) and pulmonary adverse events leading to hospitalisation (Geerts, 2013).

- **Drugs where the guidance is unspecific caution but are known to cause ADRs in reduced kidney function.** For example ACEIs or ARBs are used for patients with reduced kidney function but they need regular review and assessment of use and dose as they can be nephrotoxic.

Kidney function estimation

A substantial difference was found between estimating kidney function using eGFR (calculated using the MDRD equation, 6.9%) and CrCl (calculated using the Cockcroft Gault equation, 29.1%) for the people reviewed. For 22.2% of the 65 year olds and over, the equation used would result in a different decision being made about whether a drug could be safely used or whether a dose needed altering.

Harm caused

Examples of harm were found from drugs when kidney function was reduced. Of the 4 examples, 3 had resulted in admission to hospital. As this study did not systematically search for ADRs, the rate of harm could have been higher. Applying the recommendations readily available in the BNF and SPCs might have reduced the risk of harm.

1.3.4.2 Strengths and limitations

Consistent use of a standard method was used to review the use of medicines for 594 older people with RKF, compared with BNF and SPC recommendations. There are a number of ways that this case-note review may have not included all relevant patients and drugs. Only repeat medications were reviewed so drugs prescribed acutely such as NSAIDs and antibiotics would have been missed, and non-prescription medicine use was not assessed. Patients with a documented eGFR on their record were reviewed, but not those who have never had serum creatinine checked. The last recorded serum creatinine was used, but if it had not been checked recently, the result may not have still been relevant.

The cross-sectional assessment of the current repeat medication list did not allow for inclusion of patients who have tried medications in the past but had to stop them because of ADRs. This could be important in identifying drugs particularly causing ADRs in the reduced kidney function of the older person.

The GP practices included were in one small urban area of Bradford and so the results may not be valid in a wider population.

1.3.4.3 What this study adds to the literature

The findings of this study have been presented as a poster at the Royal Pharmaceutical Society conference 2011 and the Renal Association conference 2012, with an abstract publication from the former (Wood et al, 2011). Areas that need to be studied further include:

- What is the evidence base for prescribing for older people with RKF, including which equation should be used for drug use and dosing decisions?

- Are the case-note review findings generalisable for a wider population?

1.3.4.4 What this study adds to practice and policy

This study has highlighted that practice needs to be improved when prescribing for older people with RKF in primary care and the findings will inform further research. A quarter of older people with RKF were at risk from their medications, many drugs were implicated, and evidence of harm found. A change in practice and policy would need to be comprehensive and be able to encompass the four different categories of inappropriate use identified in this study i.e. drugs:

- To avoid.
- To reduce the dose.
- That are ineffective.
- Where caution is needed from a high risk of ADRs.

Local practice has been improved in the practice pharmacy team with kidney function assessment being added to audits for older people and greater awareness of the issues. However, it needs to be investigated in a wider population before assessing the need for a change in national policy.

1.3.5 Conclusion from the case-note review

Evidence of harm, and increased risk of harm, for older patients on drugs excreted by the kidney has been highlighted in this case-note review. A quarter of older people were prescribed at least one medication that needed altering because of their kidney function, indicating that the BNF prescribing recommendations are not followed by prescribers in primary care.

1.4 Prescribing behaviour and behaviour change

The case-note review findings led to further questions on:

- Why are recommendations for prescribing in RKF frequently not applied in primary care?
- Would an analysis of the prescribing behaviour illuminate the determinants?
- How might that behaviour be changed to reduce the risk of harm for patients?

1.4.1 Prescribing behaviour

Aronson (2006), editor of 'Meyler's Side Effects of Drugs' and chairman of the editorial board of the British Journal of Clinical Pharmacology, states that *"Prescribing is difficult. It requires a thorough knowledge and understanding of the pathophysiology of*

disease, the pharmacological properties of the relevant drugs, and the ways in which the two dovetail." Prescribing comes towards the end of a clinical decision-making process of assessment and diagnosis, where it is concluded and agreed that an intervention of a drug prescription is required, rather than 'wait and see', 'obtain more information', or an alternative intervention (Hunink et al, 2001). The World Health Organisation (WHO) (de Vries et al, 1994) recommends a systematic stepped approach to prescribing:

1. Define the patient's problem.
2. Specify the therapeutic objective.
3. Verify the suitability of the drug, the most effective, safe, suitable and cheap option.
4. Write a prescription.
5. Give information, instructions, and warnings.
6. Monitor (and stop?) the treatment.

A reduced kidney function would need to be part of the prescribing decision process at Step 3 as to whether there are any recommendations for prescribing in RKF that would mean a drug is 'unsuitable', and whether it would be 'unsafe' unless a reduced dose, or alternative were used. It would also impact on Step 6 as kidney function can change, and so it would need monitoring to ensure the drugs and dose is still suitable. The level of kidney function would need to be considered at both initiation of a drug, and at medication review.

1.4.2 Behaviour change

Behaviour change is key to improving health care and changing behaviour is more effective if interventions are developed on evidence-based principles of behaviour change (Cane et al, 2012). Designing interventions based on intuition rather than theory precludes the possibility of understanding the processes that underlie effective interventions, and of applying this knowledge to inform the design of future interventions (Abraham et al, 2009). Influencing behaviour change needs an in depth investigation of all the determinants to fully understand and explore that behaviour. Using a theoretical approach allows identification of factors and strategies that are more likely to be successful in influencing behaviour change (Nilsen, 2015). Two main issues have been identified as reducing the likelihood of success of implementation strategies (Dyson et al, 2011);

- A failure to identify barriers and enablers to implementation of evidence based practice (Grimshaw et al, 2004; NICE, 2007).

- A lack of theoretical basis for the interventions used to support the implementation of evidence into practice (Grimshaw et al, 2004; Michie et al, 2005).

Foy et al (2011) found that theories provide a way of understanding and predicting the effects of interventions intended to prevent or mitigate harm caused by healthcare, or risks of such harm. Also, theory-driven evaluations would help generalise findings to other contexts and build a cumulative understanding of the nature of change. Use of theory may explain why some implementation strategies are more effective than others (Eccles et al, 2005)

There are many theoretical models to explain behaviour change with multiple contending theories. An example is the Theory of Planned Behaviour (TPB) based on intentions and motivations (Ajzen, 1991). However, the TPB does not explore habit, emotion or working environment, for example, which may be important in prescribing. Michie et al (2005) have highlighted that such a large number of theories and theoretical constructs cannot be fully applied, critical theories might be missed, and there was a need for a method to select among them. The 'Theoretical Domains Framework' (TDF) has addressed the need for an overarching determinant framework and was developed to identify individual factors known to influence the gap between evidence based practice and the routine delivery of health care. It was constructed on the basis of a synthesis of 128 constructs related to behaviour change found in 33 behaviour change theories, including many social cognitive theories (Cane et al, 2012). The constructs are sorted into 14 theoretical domains such as knowledge, skills, goals, and beliefs about capabilities. There were originally 12 domains (Michie et al, 2005) and they were validated and restructured to 14 in 2012. (Cane et al, 2012; Michie et al, 2014). The TDF domains have been categorised to what influences capability, opportunity or motivation for the behaviour, the 'COM-B model', shown in Table 5 (Michie et al, 2011, 2014).

For any behaviour to occur there needs to be:
- Capability - knowing what to do and how to do it.
- Opportunity - the environment is conducive, both physically and socially.
- Motivation - both reflective (conscious goals and intentions) and automatic (impulses and habits).

Understanding the behaviour in context will highlight what needs to change. Interventions need to change behaviour(s) in one or more of 'capability/ opportunity/ motivation' in such a way as to put the system into a new configuration and minimise the risk of it reverting.

COM-B		TDF domains
Capability	Psychological capability	Knowledge
		Cognitive and interpersonal skills
		Memory, attention and decision process
		Behavioural regulation
	Physical capability	Physical skills
Opportunity	Physical opportunity	Environment
	Social opportunity	Social influences
Motivation	Reflective motivation	Social/ professional role and identity
		Motivations and goals
		Belief about capabilities
		Optimism
		Beliefs about consequences
	Automatic motivation	Reinforcement
		Emotion

Table 5: COM-B categories and TDF domains (Michie et al, 2014).

The TDF has been successfully applied to understand behaviour in a range of clinical areas (Francis et al, 2012). It has been used to identify key theoretical domains that are perceived to influence healthcare professionals (HCPs) to improve appropriate polypharmacy for older people in primary care (Cadogan et al, 2015), and investigation of prescribing errors among trainee doctors (Duncan et al, 2012).

Duncan et al (2012) explored beliefs among trainee doctors, including that prescribing errors were not likely to have consequences for patients, and found that seven theoretical domains were relevant: social professional role and identity, environmental context and resources, social influences, knowledge, skills, memory, attention, and decision making, and behavioural regulation. Potentially important domains were beliefs about consequences and abilities which could be targeted for an intervention. The findings show the complex nature of prescribing behaviour.

Cadogan et al (2015) found that all the theoretical domains, except 'Emotion', were considered relevant to the target behaviour of 'prescribing of appropriate polypharmacy in primary care'. This also illustrates the complex nature of the behaviour as well as the challenge faced by the researcher when developing interventions for change. The authors were able to purposefully select eight key domains that would assist HCPs in taking action in the clinical setting; they were then

able to use these to select behaviour change techniques (BCTs) for inclusion in a future intervention for prescribing for this older population..

1.5 Summary

This chapter has highlighted that assessment of kidney function is important when prescribing, as many drugs and metabolites are excreted from the body by the kidney, and RKF can increase the risk of harm. This is particularly important for older people as kidney function reduces with age. Whilst kidney function is easily measured, there is now more than one equation to calculate the estimated level: eGFR is reported by the pathology laboratories when kidney function blood tests are done and so is easily available, but not designed to inform drug dosing decisions; CrCl-CG has historically been used for drug dosing decisions, and has been used by drug companies for dosing studies and reported in the drug SPCs. A case-note study has found that many older people are prescribed drugs that are not recommended at their level of kidney function, and has suggested that using eGFR or CrCl-CG gives different results in older people. This suggested a need to explore further to find if there is supporting evidence in the literature for which equation should be used for prescribing for older people.

The pilot study in primary care reported in this chapter has suggested that recommendations for prescribing in RKF are not applied, and an investigation in a wider population might show if this finding is generalisable, and whether an intervention is needed to help prescribers.

An analysis of the complex prescribing behaviour, and an exploration of the determinants, could provide an in-depth understanding of the factors involved in recommendations for prescribing in RKF not being applied. If a change in prescriber behaviour is found to be needed to reduce risk of harm for patients, it is more likely to be effective if an intervention is developed on theory and evidence based principles of behaviour change.

The questions raised informed the mixed methods research plan.

1.6 Research Plan

1.6.1 Methodology

A pragmatic sequential mixed methods design (Robson, 2011) was proposed to produce a comprehensive picture of prescribing for older people with RKF in primary care. From the case-note review, the inquiry would be driven by the research questions, and derived from the integration of methods and results from the previous studies (Bazeley, 2009). The programme of research was planned to combine both quantitative and qualitative methods, and resulting data, to address the different research questions and enhance the validity of the findings (Cresswell, 2009; Robson, 2011).

1.6.2 Research question

Are recommendations for prescribing applied for older people with reduced kidney function in primary care, and if not, what are the barriers to implementation?

1.6.3 Aims

The aims of this mixed methods programme of research were to:

- Systematically determine the size and nature of the current evidence base on prescribing for older people with reduced kidney function, identify any gaps in the literature, and use this to inform the ongoing research plan.

- Investigate whether recommendations for prescribing in reduced kidney function (RKF) were being applied for older people across a (former) Primary Care Trust (PCT) population.

- Explore why GPs do not apply the drug licence recommendations when prescribing for older people with reduced kidney function.

- Prioritise a strategy for intervention and research.

1.6.4 Research plan

The sequential research plan and chapter numbers are shown in Figure 6. To provide an overview, the research questions, data collection and analysis procedures for this mixed methods project are presented in Table 6.

1.6.5 Funding and support

This research project has been self-funded and supported by the Academic Unit of Pharmacy, Radiography and Healthcare Science, and the Leeds Institute of Health Sciences, University of Leeds.

Cross-sectional case-note review in 5 GP practices (Chapter 1)

Scoping literature review (Chapter 2)

Primary Care Trust–wide cross-sectional survey of prescribing data (Chapter 3)

Qualitative GP interview study (Chapter 4)

Consensus group study (Chapter 5)
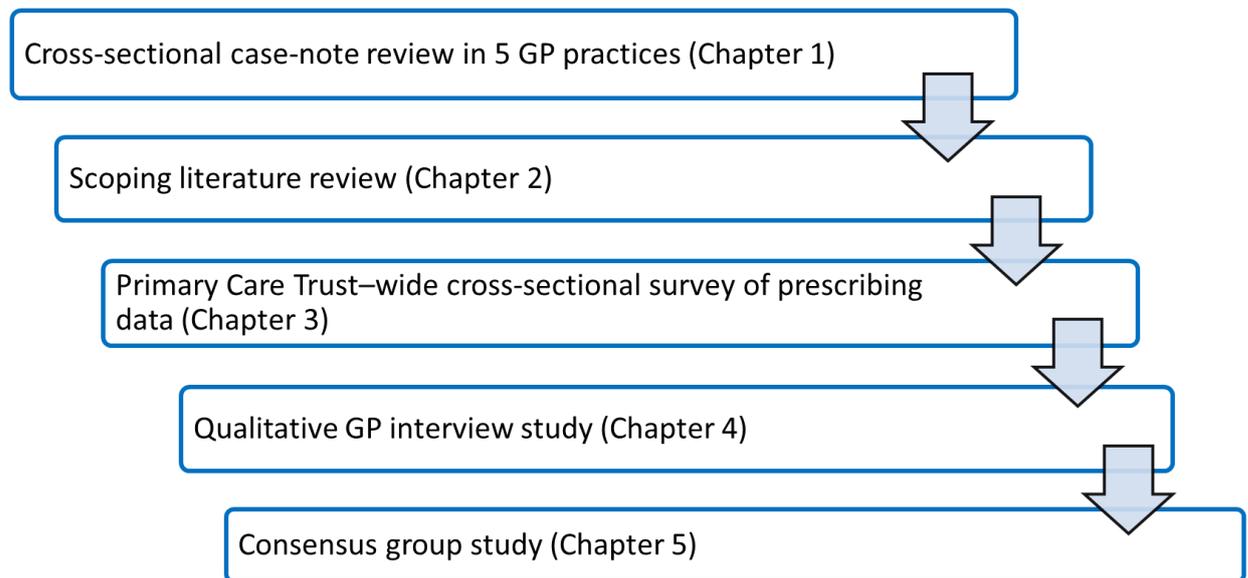
Figure 6: The sequential mixed methods research plan.

chapter	method	research questions	theoretical/ conceptual basis	data sources	data analysis	integration
1	Cross-sectional Case-note Review	Are recommendations for prescribing in reduced kidney function being applied in 5 GP practices?	Variable relationship testing.	Case-note review.	Quantitative descriptive analysis.	• Provided the basis for the subsequent studies in the project.
2	Scoping Literature Review	What is the size and nature of the evidence base on prescribing for older people with reduced kidney function in primary care, are there gaps in the literature, and what future primary research is needed?	Arksey & O'Malley scoping literature review.	Research databases.	Framework analysis in 6 key areas.	• 6 key areas to review based on the Case-note Review findings • Update in 2015, and analysis, led to re-analysis of the PCT survey data.
3	PCT-wide Cross-sectional Survey	Are drugs, that require kidney function assessment, prescribed according to recommendations for use in reduced kidney function for people aged 65 years and older across a PCT population?	Variable relationship testing.	PCT wide prescribing data.	Quantitative descriptive analysis.	• Variables tested based on those found in the Case-note Review. • Methods and variables informed by similar studies from hospital and other countries found in the Scoping Literature Review. • Re-analysis of data to give 'cases missed', after Scoping Review update.
4	Qualitative GP interview study	Why are prescribing recommendations not applied for older people with reduced kidney function in primary care?	Behaviour change theory - theoretical domains framework.	GP interviews.	Qualitative TDF analysis.	• Participant pre-reading and topic guide based on the findings from the Case-note Review and PCT-wide survey.
5	RAND Appropriateness method Consensus Group Study	Do experts in fields relating to prescribing in reduced kidney function find the evidence from the four project studies generalisable, acceptable, and feasible for an intervention, and what are the priorities future research?	Behaviour change theory - TDF.	Consensus group questionnaire on-line survey, group discussion, and final statement rating.	Quantitative descriptive analysis and a qualitative TDF analysis.	• Statements for rating based on the GP interview study findings. • Group discussion based on the Case-note Review, Scoping Literature Review, PCT-wide Survey, and GP Interview studies. • Continued use of the TDF working from the GP Interview study.

Abbreviations: PCT: Primary Care Trust; TDF: Theoretical Domains Framework

Table 6: Research questions, data collection and analysis procedures for this mixed methods project.

'The use of drugs in patients with impaired renal function can give rise to problems for several reasons….many of these problems can be avoided by careful choice and use of drugs.'

The Renal Drug Handbook 4th Edn (Ashley & Currie (Eds), 2014)

2 Chapter 2: A scoping literature review to identify the evidence base on prescribing for older people with reduced kidney function

2.1 Background

A quarter of people aged 65 years and older with reduced kidney function (RKF) were prescribed a drug that is recommended to be avoided, or the dose reduced, and evidence of harm was found in the case-note review in 5 GP practices in Bradford (Chapter 1). Also highlighted was that there are two different kidney function estimation equations, creatinine clearance calculated using the Cockcroft Gault equation (CrCl-CG) and eGFR calculated using the MDRD equation which gave different results for older people. For 22% of the older people reviewed, the prescribing decision would have been different depending on which equation had been used.

This study aimed to review the literature and systematically determine the size and nature of the current evidence base for prescribing to older people with reduced kidney function, identify gaps in the literature, and inform the ongoing research plan.

2.2 Research question and objectives for the literature review

Research question

What is the size and nature of the evidence base on prescribing for older people (≥65 years) with reduced kidney function in primary care, whether there are there gaps in the literature, and what future primary research is needed?

Objectives

- To outline what is already known, and identity gaps in the existing literature, on the prevalence of prescribing for older people with reduced kidney function in UK primary care.
- To formulate the key areas for review of the evidence base in this field.

- To investigate the extent, range and nature of any research in each key area, quantitative or qualitative as appropriate.
- To consolidate the research plan.

2.3 Methodology

A comprehensive, and systematic, mapping of the literature for a broad topic was the aim of this study, so the required breadth needed to answer the research question suggested a 'scoping literature review' methodology. The Centre for Reviews and Dissemination at York University (2009) state that 'a scoping review determines the size and nature of the evidence base for a particular topic area, which can in turn be used to identify gaps in the literature and make recommendations for future primary research'. The literature search should be as extensive as possible, but it differs from standard systematic reviews in that a scoping review does not attempt to synthesise the evidence and that it is not appropriate to use a scoping review to answer a clinical question. Armstrong et al (2011) from the Cochrane Public Health Group state that published scoping reviews are a valuable resource that can be of use to researchers, policy-makers and practitioners, reducing duplication of effort and guiding future research. A scoping review methodology was used for this study as the aim was not to answer a precise question, but to explore the range of literature in the area of prescribing for older people with reduced kidney function.

A key methods paper for scoping reviews is the methodological framework by Arksey and O'Malley in 2005. Levac et al (2009) has since provided recommendations to clarify and enhance each stage, which may increase the consistency with which researchers undertake and report scoping studies. Clarifying and linking the purpose and research question, balancing feasibility with breadth and comprehensiveness of the scoping process, and identifying the implications of the study findings for policy, practice, or research were suggested.

Arksey and O'Malley state that a key strength of the scoping study is that it can provide a rigorous and transparent method for mapping areas of research. It provides a 'narrative' or 'descriptive' account of available research. However, the limitations are that a scoping review does not formally appraise the quality of evidence and there can be a large quantity of data generated leading to decisions on breadth versus depth. Levac et al (2009) discusses the need to assess included studies for methodological quality, and Brien et al (2010) state that a lack of quality assessment makes the results of scoping studies more challenging to interpret. Grant and Booth (2009) imply that a lack of quality assessment limits the uptake of scoping study findings into policy and

practice, but Levac concluded that it remains unclear whether not including quality assessment impacts the uptake and relevance of scoping study findings. An assessment of the quality of the included studies would give an indication of where the current literature is of sufficient quality to answer the research question, or if there is a need for further, higher quality, investigation to have greater confidence in the findings. Levac states that it is a challenge to assess quality among the vast range of published and grey literature that may be included in scoping studies. By including a quality assessment, to be feasible there necessarily needed to be a reduction in the scope of the searches, so only published studies were included, and opinion and discussion articles were excluded. Inclusion of only published empirical literature introduces the risk of publication bias, by not assessing the effect of unpublished studies that are more likely to be negative, and by a reduction in the breadth of the investigation.

Studies were charted as described in the Arksey & O'Malley framework. Appropriateness of study design and study quality were assessed. A hierarchy of evidence was developed for each scoping review area based on the Oxford Centre for Evidence-Based Medicine (OCEBM) levels of evidence (Oxford Centre for Evidence-Based Medicine, 2011) (Table 7). The table shows the 'Step 1', or 'Level 1', types of studies that are likely to give the highest level of evidence for the type of question posed, reducing down to 'Step 5', or 'Level 5', for the study designs that would give the lowest degree of confidence in the results. Levels of evidence were developed for each scoping area based on the research question and adapted from Table 7. This was an iterative process with additional levels being added where required having reviewed the studies found.

The studies were also critically appraised using the Critical Appraisal Skills Programme (CASP) checklists for appraising systematic reviews, randomised controlled trials (RCTs), cohort studies, case-controlled studies, and qualitative research, the Centre for Evidence Based Management (CEBM) checklist for surveys, and in addition the 'Consolidated criteria for reporting qualitative research' (COREQ) for appraisal of the qualitative studies. The checklists aided assessment of whether the conclusions of each study were valid in that they were supported by the results presented and consistent with the methods used, and the reported detail of the methods were sufficient to repeat the study and obtain similar conclusion.

Question	Step 1 (Level 1*)	Step 2 (Level 2*)	Step 3 (Level 3*)	Step 4 (Level 4*)	Step 5 (Level 5)
How common is the problem?	Local and current random sample surveys (or censuses)	Systematic review of surveys that allow matching to local circumstances**	Local non-random sample**	Case-series**	n/a
Is this diagnostic or monitoring test accurate? (Diagnosis)	Systematic review of cross sectional studies with consistently applied reference standard and blinding	Individual cross sectional studies with consistently applied reference standard and blinding	Non-consecutive studies, or studies without consistently applied reference standards**	Case-control studies, or "poor or non-independent reference standard**	Mechanism-based reasoning
What will happen if we do not add a therapy? (Prognosis)	Systematic review of inception cohort studies	Inception cohort studies	Cohort study or control arm of randomized trial*	Case-series or case-control studies, or poor quality prognostic cohort study**	n/a
Does this intervention help? (Treatment Benefits)	Systematic review of randomized trials or n-of-1 trials	Randomized trial or observational study with dramatic effect	Non-randomized controlled cohort/follow-up study**	Case-series, case-control studies, or historically controlled studies**	Mechanism-based reasoning
What are the COMMON harms? (Treatment Harms)	Systematic review of randomized trials, systematic review of nested case-control studies, n-of-1 trial with the patient you are raising the question about, or observational study with dramatic effect	Individual randomized trial or (exceptionally) observational study with dramatic effect	Non-randomized controlled cohort/follow-up study (post-marketing surveillance) provided there are sufficient numbers to rule out a common harm. (For long-term harms the duration of follow-up must be sufficient.)**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning
What are the RARE harms? (Treatment Harms)	Systematic review of randomized trials or n-of-1 trial	Randomized trial or (exceptionally) observational study with dramatic effect			
Is this (early detection) test worthwhile? (Screening)	Systematic review of randomized trials	Randomized trial	Non-randomized controlled cohort/follow-up study**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning

* Level may be graded down on the basis of study quality, imprecision, indirectness (study PICO does not match questions PICO), because of inconsistency between studies, or because the absolute effect size is very small; Level may be graded up if there is a large or very large effect size.

** As always, a systematic review is generally better than an individual study.

Table 7: The hierarchy of evidence from the Oxford Centre for Evidence-Based Medicine (2011)

CASP gives the three broad issues to be considered when appraising a study report as:

- Are the results valid i.e. does the study provide an unbiased estimate of what it claims to show?
- What are the results?
- Will the results help locally?

The screening questions provided in the checklists were used to appraise each included study.

2.4 Study design

2.4.1 Method

The framework proposed by Arksey and O'Malley (2005), with the Levac et al (2009) recommendations, has been used to conduct and structure the literature review to provide a rigorous, robust and reproducible method.

Once initial search plans and criteria had been drafted, advice was sought from Mark Clowes (University of Leeds Health Library Services) to ensure the search terms and strategies were comprehensive enough to find the relevant literature. One researcher (myself) conducted all stages of the scoping literature review.

2.4.1.1 Stage 1: identify the key areas for review and the research question for each

Arksey and O'Malley recommend maintaining a wide approach to ensure breadth of coverage, and that parameters can be set once the scope of the field has been assessed. The findings from the case-note review (Chapter 1) were interrogated using a mind map approach to identify the key areas for review and the research question for each.

Figure 7 is the mind map showing the case review findings leading to the six key areas for review:

1. To what extent are older people (≥65 years) on drugs and doses not recommended at their level of kidney function in primary care?

2. How should kidney function be estimated when prescribing for older people in primary care?

3. What are the risks to the older person in primary care of not following the recommendations for prescribing in reduced kidney function?
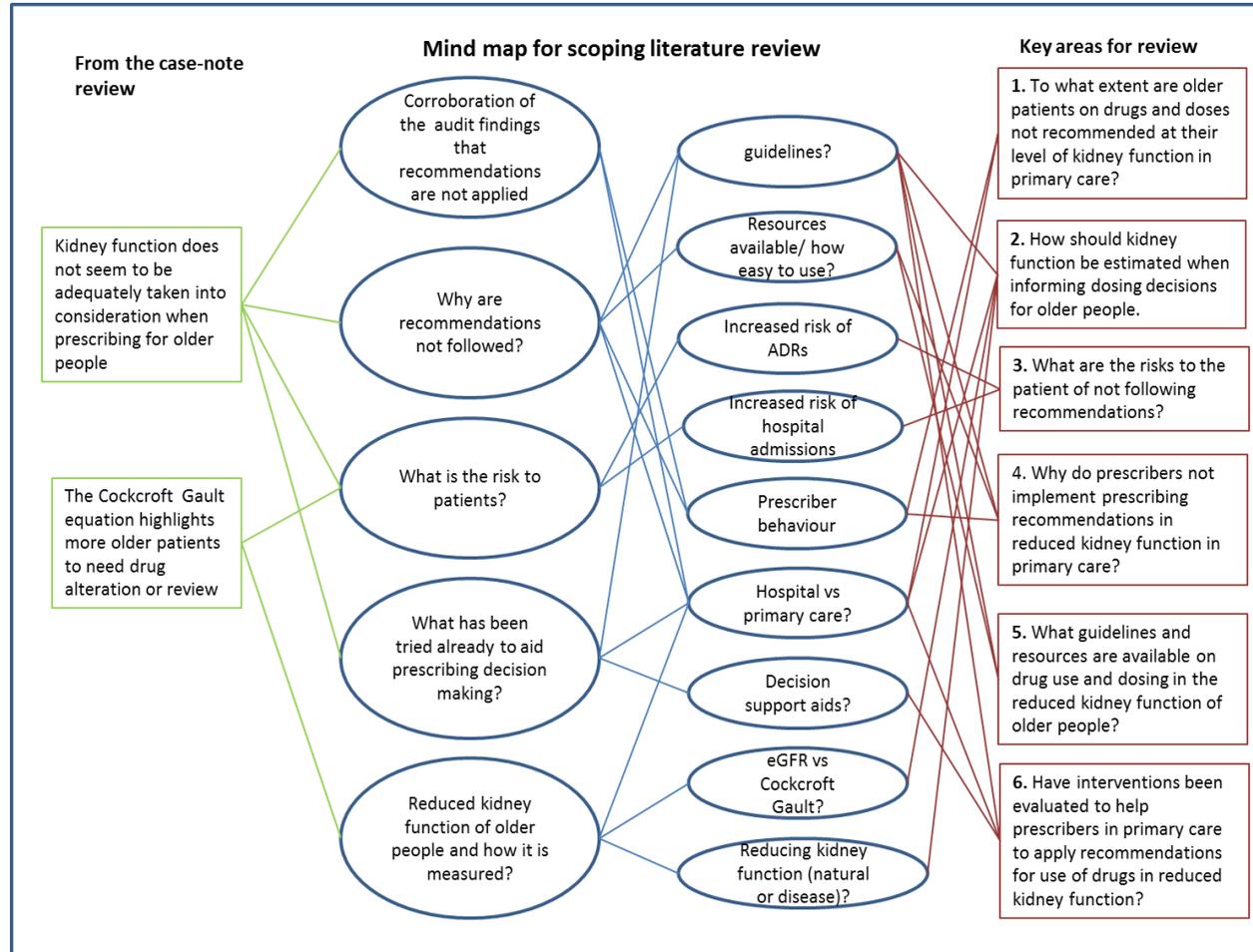
Abbreviations: ADRs: adverse drug reactions; eGFR: estimated glomerular filtration rate.

Figure 7: Mind map to identify key areas for the scoping literature review from the case-note review findings.

4. Why do prescribers not apply prescribing recommendations in reduced kidney function in primary care?

5. What UK national guidelines and resources are available on drug use and dosing in the reduced kidney function of the older person?

6. Have interventions been evaluated to help prescribers in primary care to apply recommendations for use of drugs in reduced kidney function?

The development of the research questions was an iterative process and only fully defined through the initial literature search.

2.4.1.2 Stage 2: identify relevant studies for each key area for review

The aim was to be as comprehensive as possible. The literature for key areas 1,2,3,4, and 6 was identified by database literature searches. For key area 5, guidelines and resources were identified through expert advice (renal, elderly care, clinician and pharmacist). For each key area the review was based on stages defined by Hagell and Bourke Dowling (1999).

The database searches were first run between October 2011 and March 2012. They were then re-run in October 2012 to update for the transfer report, and updated again in October 2015.

A preliminary map of the issues in the area.

The case-note review findings, mind mapping, and an initial unstructured search of the literature identified the relevant topics.

Research reviews

The Cochrane Library database of systematic reviews was searched to identify any reviews relating to prescribing for older people with reduced kidney function in the 6 key areas. The Database of Abstracts of Reviews of Effects (DARE) was also checked for existing or ongoing reviews. Research reviews were searched for in Medline and then highlighted from each database searched.

Database search

The search for each key area aimed to comprehensively identify relevant studies, and was run on each of the following databases: Medline, Embase, PsychINFO (for the psychological perspective on healthcare), CINAHL (for a nursing perspective), and Web of Science.

The search terms for each key area were set up using the following categories where appropriate. Appendix 3 (0) details the subject headings, and key word, search terms, and synonyms under each of the following categories:

- Prescribers (which includes physician as well as the misspelling 'phycisian' as the library expert advised it can find more studies being a term that is frequently misspelled). Non-medical prescribers were included by the use of the term 'prescriber'.
- Prescribing.
- Guidelines/recommendations (which includes 'guidance' and the misspelling 'guideance').
- Primary Care.
- Renal impairment.
- Elderly.
- Adverse drug reactions (ADRs).
- Decision support tools.
- Prescriber Behaviour.
- Kidney function Equations/diagnostic tests.
- Additions – English language/reviews/qualitative.

Within each category the synonyms were searched using 'OR'. The relevant categories were then used in the searches for each key review area using 'AND'. An example of a Medline search strategy is given in Appendix 4 (8.3) for key review area 4.

Type of research for each key area

The type of research searched for is dependent on the research question and is discussed under each key area section (2.4.1.2 - 0).

Reference organisation

EndNote X5 was used to organise and manage the references found for each key area and background to the research.

2.4.1.3 Stage 3: study selection for each key area for review

By aiming to keep the search sensitive, in order to be comprehensive, specificity can be reduced so that many irrelevant studies are picked up. To eliminate irrelevant studies inclusion and exclusion criteria were developed and listed under each key area section.

The resultant list of articles found for each search were initially reviewed by title and abstract. The selected articles were exported to EndNote and then the abstracts reviewed having removed any duplicates. Full text copies were obtained for the studies identified to be included for review.

2.4.1.4 Stage 4: chart the data

The significance of the included studies was then considered, and the quality assessed. A data charting form was developed based on the criteria used by Arksey and O'Malley (2005) to collect:

- Author(s), year of publication, study location.
- Intervention type and comparator (if any); duration of intervention.
- Study populations.
- Aims of study.
- Methodology.
- Outcome measures.
- Important results.

The form also listed the CASP screening questions to aid appraisal. All studies identified for review were charted. This stage allowed further scrutiny as to whether the study fitted the search criteria, or whether the search criteria needed amendment.

The level of evidence for the review area question was also assessed, and the selected literature appraised. The OCEBM Levels of Evidence applicable to the research question were used to develop a hierarchy of evidence table, adapted for each key review area (Oxford Centre for Evidence-Based Medicine, 2011). Each study was then assessed for level of evidence and methodological quality using the relevant checklists (CASP, CEBM or COREQ), which was added to the charting process, and allowed ordering of the included studies.

2.4.1.5 Stage 5: collate, summarise, and report the results

The final literature to be included in each key search area was assessed and the findings scrutinised. The studies were categorised and evaluated for common themes and findings to collate and summarise the results of the review.

2.4.1.6 Stage 6: consultation (optional)

Arksey and O'Malley (2005) discuss an optional final stage of consultation so that practitioners and consumers can contribute to the work. They state that contributors can provide additional references and valuable insights about issues that the scoping review alone may not provide. Time limits have meant that this stage has not been included, but a consultation is intended before publication.

2.4.2 Ethics and governance

As a literature review with no participant involvement, no ethics or governance approval was required.

2.5 Key review area 1 – evidence on whether prescribing recommendations are applied for older people with reduced kidney function in primary care.

2.5.1 Research question for key review area 1

To what extent are older people (≥65 years) on drugs and doses not recommended at their level of kidney function in primary care?

2.5.2 Identification of relevant studies - search criteria

The search categories were 'Prescribing' AND 'Renal impairment' AND 'Elderly' AND 'Primary Care' AND English language (see Appendix 3, 0, for the subject headings and key words for each search category). The search term 'review' was added to the Medline search to highlight any relevant review papers.

2.5.3 Study selection – inclusion/exclusion criteria

The research question is focussed on primary care, however other healthcare settings were included in case the primary care evidence was limited, and for comparison. No date range was applied to the searches so that the scope would include studies from prior to the introduction of the national CKD guidelines in 2005.

Study selection from the search results were based on the following criteria:

Inclusion

- English language.
- Primary empirical research and reviews.
- Outcome relating to assessment of compliance with prescribing recommendations in reduced kidney function.

Exclusion

- Opinion or discussion articles.

2.5.4 Hierarchy of evidence and appraisal

The research question asked 'how common is the problem?' so the OCEBM Levels of Evidence (2011) gives the 'Level 1' evidence, which would give greatest confidence in the findings, to be 'local and current random sample surveys (or censuses)'. If good level 1 evidence is not found then studies of lower level relevance, and non-local evidence, would give an insight into whether further research is needed. Table 8 lists the hierarchy of evidence developed for key review area 1 based on the OCEBM

Levels of Evidence. Non-local levels have been added, and a grade 'b' where the evidence is not current or not based in primary care, which would reduce the external validity for current UK primary care.

hierarchy of evidence	description
Level 1	Local and current random sample surveys (or censuses)
Level1b	Local random sample surveys (or censuses) - not current/ not primary care
Level 2	Systematic review of surveys that allow matching to local circumstances
Level 2b	Systematic review of surveys that allow matching to local circumstances - not current/ low quality for primary care
Level 3	Local non-random sample
Level 4	Local case series
Non-local level 1	Non-local and current random sample surveys (or censuses)
Non-local level 1b	Non-local random sample surveys (or censuses) - not current/ not primary care
Non-local level 3	Non-local non-random sample
Non-local level 3b	Non-local non-random sample - not current/ not primary care
Non-local level 4	Non-local case series
Non-local level 4b	Non-local case series - not current/ not primary care

Table 8: Hierarchy of evidence table for key review area 1 'how common is the problem?' developed from the OCEBM Levels of Evidence.

The issues considered when appraising the report of a descriptive survey were whether 'the results of the study were valid, what were the results, and would the results help locally', as defined by critical appraisal tools such as the CASP. For this review, 'locally' would be applicability to UK primary care. To aid the quality assessment the CEBM 'Critical Appraisal of a Survey' tool was used (Centre for Evidence Based Management). For other study designs, the CASP 'Study checklists' informed the review. Studies were assessed and only included where the focus, methods, recruitment and sampling, valid and reliable objective measurements used, and outcomes were clearly defined, relevant and appropriate to the research question.

2.5.5 Collation and appraisal
2.5.5.1 Description of studies

Twenty-five relevant studies were identified from the database searches (Figure 8) that aimed to investigate the extent to which drugs and doses prescribed are not recommended at their level of kidney function. Table 9 lists the included studies in order of the level of evidence they provide.

| Screened by title | Medline 6,242 | Embase 13,839 | PsychInfo 73 | CINAHL 2,021 | Web of Science 500 | Cochrane DARE 0 |

Screened by abstract, and de-duplicated → 25
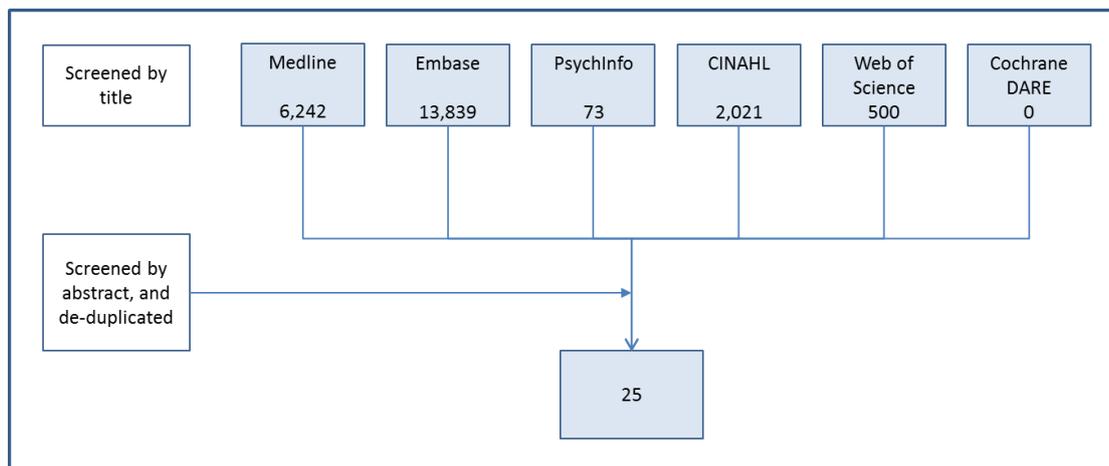
Figure 8: Number of studies identified for key review area 1.

CKD guidelines began to be published in the early 2000's, in the UK it was 2005 when the first were introduced (Joint Specialty Committee for Renal disease of the Royal College of Physicians of London and the Renal Association, 2005), and most of the studies date from that time onwards, suggesting an increased awareness of kidney function in relation to prescribing. The earlier studies were all hospital based, with the first primary care study being published in 2005.

The OCEBM Levels of Evidence for prevalence studies suggest that local studies are the most appropriate and applicable (Oxford Centre for Evidence-Based Medicine, 2011), but only two UK based studies other than the Chapter 1 case-note review were found, and those were hospital based. There were no geographical limits put on the scoping review searches and most studies were based in countries that might be considered to have similar populations to the UK, although the healthcare systems may be different, for example the USA (x4), Australia (x2), Canada (x1), and Western Europe (x11) (see Table 9). Four studies were from differing populations, and were all hospital based, South Africa (Decloedt et al, 2010), Iran (Emami et al, 2012), South Korea (Sheen et al, 2008), and Palestine (Sweileh, 2007). These studies, that report a similar range of substantial non-compliance rates with prescribing guidelines, suggest it should be recognised as a multi-national problem.

Only seven studies found were based in primary care, and none in the UK other than the case-note review. The prescribing systems and procedures are different to those in hospitals, including advanced computerised patient record systems used in UK primary care that could mean different findings to hospital based studies.

principal author	hierarchy of evidence (based on OCEBM)	year	country	study type	prospective, cross-sectional, or retrospective	setting	participant numbers	participant type	outcomes
Wood	Level 1	2011	UK	survey	cross-sectional	primary care	594	≥65yrs	25% had repeat medication that was inappropriate for their level of kidney function.
Jones	Level 1b	2013	UK	survey - case review	retrospective	hospital	100	> 70 years with eGFR <60 ml/min/1.73m^2	56% of consecutive cases were prescribed at least one medication that was potentially inappropriate.
Wong	Level 1b	1998	UK	cohort	retrospective	hospital	1162	discharged from geriatric ward with CrCl <20 ml/min	20% with CrCl 10-20ml/min had drug prescriptions on discharge that contradicted the BNF recommendations, and 67% of those with CrCl<10ml/min.
Long	Level 2b	2004	USA	systematic literature review	mixed	mixed	6 studies included		Renal dosing guideline non-compliance rates ranged from 19-69% across all settings with the largest in ambulatory care.
Breton	Non-local level 1	2011	France	cohort	prospective	primary care	8,701	≥65yrs	13.3% overall prevalence of inappropiate drug use in RKF.
Schmidt-Mende	Non-local level 1	2012	Sweden	survey	cross-sectional	primary care	3,345	≥65 years with hypertension	48% drugs prescribed were potentially inappropriate.
Khanal	Non-local level 1	2015	Australia	survey	retrospective	primary care	4,035	≥65yrs	28.1% had inappropriate prescribing of the 31 drugs analysed; only 25% had a documented kidney function.
Emarmi	Non-local level 1b	2012	Iran	survey	prospective	primary care	193 prescriptions which would need dose adjustment	eGFR ≤50 ml/min/1.73m^2 on a drug that might need adjustment	23.2% of orders written for patients with varying degrees of renal impairment required adjustment but were performed in only 45.5% of these cases.
Yap	Non-local level 1b	2005	USA	survey	retrospective	primary care	224	<50ml/min	25% were prescribed an inappropriately high dose.
Blix	Non-local level 1b	2006	Norway	cohort	prospective	hospital	515	medical admissions with eGFR<60 ml/min/1.73m^2	17% of drugs on admission, and 34% of drugs started in hospital, needed dose adjustment.
Decloedt	Non-local level 1b	2010	South Africa	survey	prospective	hospital	97	eGFR ≤50 ml/min/1.73m^2	71% received one or more drugs that required dose adjustment.
Falconnier	Non-local level 1b	2001	Switzerland	case control	prospective	hospital	1648	eGFR ≤50 ml/min/1.73m^2 on a drug	67% regimens not adjusted in RKF in the control group.
Sheen	Non-local level 1b	2008	South Korea	survey	retrospective	hospital	431,119	prescriptions	Overdose rates: 1.3% mild RKF, 27.8% moderate RKF, 29% severe RKF.
Cantu	Non-local level 3b	1992	USA	survey	prospective	hospital	60	CrCl <40 ml/min	45% were receiving dosages in excess of the manufacturers' recommendations.
Drenth van Maanen	Non-local level 3b	2015	Netherlands	cohort	retrospective	hospital	1,327	eGFR 10-50 ml/min/1.73m^2 prescribed defined drugs	46% non-adherence with the Dutch dosing in RKF guideline.
Falconnier	Non-local level 3b	2001	Switzerland	case-control	prospective	hospital	70	CrCl <50 ml/min and on a drug	67% did not have doses adjusted to renal function.
Gibert	Non-local level 3b	2013	France	survey	cross-sectional	hospital	412	≥75 years	When kidney fuction calculation was present, an inappropriate dosage was performed for 30% of drugs requiring adjustment.
Hu	Non-local level 3b	2001	USA	survey- chart review	retrospective	hospital	1,044	> 80 years prescribed the study antibiotics	Dosing errors were identified in all of the antibiotics studied; overall dosing error rate was 34%; factors predictive of dosage errors were advanced age and low body weight
Pillans	Non-local level 3b	2003	Australia	survey	prospective	hospital	192	CrCl <40 ml/min prescribed defined drugs	42.2% of doses were inappropriately high on admission, and 29.3% were continued
Salomon	Non-local level 3b	2003	France	survey	prospective	hospital	164	inpatients with a raised SrCr	34% were inappropriate, 14% being contra-indicated and 20% with inappropriate dosage given the patient's renal function.
Sweileh	Non-local level 3b	2007	Palestine	survey	cross-sectional	hospital	78	CrCl <60ml/min prescribed at least 1 drug	74% of relevant drugs were prescribed inappropriately.
Van Dijk	Non-local level 3b	2006	Netherlands	survey	retrospective	hospital	237	eGFR <51 ml/min/1.73m^2	79.3% had 1 or more drugs needing dosage adjustment, 23.9% of prescriptions.
Vanier	Non-local level 3b	2011	France	survey - note review	retrospective	hospital	170	≥65yrs	Concordance for renal function was required for 82.9%, for at least one prescription.
Farag	Non-local level 4	2014	Canada	case series	prospective	primary care	1,464 prescriptions	≥66yrs with CKD 4-5	64% antibiotics prescribed where kidney function was too low.
Ingrasciotta	Non-local level 4	2014	Italy	case-series	retrospective	primary care	1,989	diagnosis of CKD	49.8% prescribed 1 or more nephrotoxic drugs; 35.6% had NSAIDs for > 3 months.

Abbreviations: CrCl: creatinine clearance; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; NSAID: non-steroidal anti-inflammatory; RKF: reduced kidney function; SrCr: serum creatinine.

Table 9: Studies found for scoping review area 1, listed in order of level of evidence.

Also the hospital patients would be likely to be acutely ill, and the drugs studied might be for acute conditions making these studies less applicable to primary care. All the primary care studies found dated from 2011, suggesting a recent awareness about prescribing in RKF.

The research question was to focus on prevalence in older people, and 9 of the studies had older participants only. Other studies were included as many discussed that older people are more likely to have reduced kidney function, and statistical analyses in some highlighted old age as a 'risk factor'. For some studies without defined age inclusion or exclusion criteria, the study populations were reported to have mean ages over 65 years; for example, mean ages of 70 years (Salomon et al, 2003), 73 years (Pillans et al, 2003), and 75 years in the Flaconnier et al (2001) study.

2.5.5.2 Heterogeneity

The included studies showed considerable variation in the characteristics of healthcare settings, patients versus prescriptions, drugs studied, and kidney function measurement and estimation. Where it was defined that older people would be studied, there were age thresholds of 65 year and older (x4 studies), ≥66 years, >70, ≥75 and over 80 years (Table 9). All the studies clearly defined the way kidney function was recognised, measured and levels estimated, but many different methods and thresholds were used: CKD stages 3-5 or 4-5; eGFR <40, ≤50, 10-50, <60 ml/min/1.73m^2; CrCl <20, <40, <50, and <60 ml/min. The subjects for most of the studies were patients, but two studies (Emami et al, 2012; Sheen et al, 2008) focussed on the drugs prescribed. Most of the studies assessed any drugs that might need dose adjustment in RKF, but some studies were more defined, for example Hu et al (2001) looked specifically at antibiotic prescribing, whilst Drenth van Maanen et al (2015) and Khanal et al (2015) had a defined list of drugs. Schmidt-Mende et al (2012) only looked at patients with a diagnosis of hypertension.

As a consequence of the wide variation, it is inappropriate to make direct comparisons, or pool data. The studies were reviewed by healthcare setting.

2.5.5.3 Methodological quality

Use of the OCEBM hierarchy of evidence levels reveals that only four of the studies would be considered as relevant to a local UK population, and three of those were hospital-based rather than primary care, or not recent and so may no longer reflect what is currently happening (Table 9). The research question was focussed on primary care, however other healthcare settings were included in case the primary care evidence was limited, and for comparison; inclusion of international studies has

allowed review of the evidence in many different countries and healthcare settings. Three studies were classified as 'Non-local Level 1' where CEBM survey appraisal suggested acceptable or good quality primary care based design and reporting. Khanal et al (2015) reported that 25% of their retrospective sample on a decision support database of 30,898 elderly patients (aged 65 years or over) had a recorded kidney function level. Those who had their renal function reported (n = 7,625) were selected for further analysis, and out of these, a total of 4,035 patients who were taking at least one of the 31 renally cleared drugs on their defined list were included in the final sample. For the other 75% of the database population it was not reported how many were taking the 31 drugs, and so total in the population could not be assessed. The studies that used CKD or eGFR, for example, to identify their study population, would not be able to show the degree to which they might be missing cases that should be assessed. Some studies analyse the participants who were excluded to show that they were similar to the study population, but it is still unknown what the kidney function levels are for that group, and whether it might change the findings of the study, introducing the possibility of bias. However, these studies do show that even with a kidney function test available, prescribing was not adjusted.

Most of the studies found were designed as surveys and they were included for review as they met most or all of the criteria required of a survey by the Centre for Evidence Based Medicine. A well designed cross-sectional survey in a local setting is likely to give the best evidence for a prevalence study as it provides a locally applicable picture of relevant data. Lower quality evidence may introduce biases that reduce the confidence in the findings being applicable. If the survey is not local, does not have a similar population, or if it was completed so long ago that circumstances may have changed, then the findings are less likely to be applicable. The cohort, case control and case series studies were not specifically designed to assess prevalence, although prevalence was an outcome reported. The longitudinal studies may have attrition bias if not all patients are followed up to the end, and the retrospective studies may have missing data from selection bias and information bias where the exposure, record keeping or outcome assessment cannot be controlled.

2.5.5.4 Prevalence outcomes: level 1 evidence UK primary care

No studies, other than the pilot study case-note review (Chapter 1; Wood et al, 2011), were found to provide current local evidence of the extent to which older people are on drugs and doses not recommended at their level of kidney function in UK primary care. This study found 25% of people aged 65 years or older with documented RKF were on at least one repeat medication that was inappropriate for their level of kidney function.

The limitations of this study, such as the being based in one small urban area of Bradford meaning that the results may not be generalisable in a wider population, and the design leading to only those with a kidney function test on the record being included, suggest that a prevalence study in a wider population would provide greater confidence on the extent of the problem generally in UK primary care.

2.5.5.5 Prevalence outcomes: reviews

Only one prevalence review paper was found, Long et al (2004). It reported a robust method but is now over ten years old and only found six studies for inclusion. None of the studies were large and the studies showed considerable variation in setting, design and population. The studies, published between 1996 and 2002, included four of the hospital based studies found for the current review, Cantu et al (1992), Falconnier et al (2001), Hu et al (2001), and Wong (1996). The other two were a care home study from Canada reporting a non-compliance with prescribing recommendations rate of 34%, and the ambulatory care pilot study was an abstract from the USA indicating a 69% non-compliance. The authors suggest the paucity of evidence found suggested a need for more research, particularly for ambulatory care settings where the majority of patients with reduced kidney function receive care.

2.5.5.6 Prevalence outcomes: primary care evidence from other countries

The French primary care study by Breton et al (2011) was of high methodological quality, and as the population is likely to be similar to the UK, the findings could be considered in relation to the UK. It is a prospective cohort study so selection and information biases should be reduced as missing data is less likely, and the exposure, record keeping and outcome assessments can be controlled. However, as it is longitudinal, it is sensitive to drop out of participants over time (attrition bias) (Green et al, 2011). This was a multi-centre trial in three cities designed to focus on prescribing for older people with RKF in primary care and included 8,701 participants with only 8 lost to follow-up when they assessed mortality at 6 years, so attrition bias was very low. Although recruitment was for all those with an available baseline eGFR, they compared the population with those without an eGFR to show that they were similar populations. There was an objective validated measurement of kidney function, a clear and objective procedure for assigning an eGFR threshold for all prescribed drugs, all subjects were classified using the same procedure, and there was detailed a reliable system for detecting exposure. There was no blinding, but confounding factors were taken into account by use of logistic regression and mortality hazard ratios, both crude and adjusted for many factors such as socio-demographic variables, cardiovascular

disease or risk, and co-morbidities. Exposure to the risk of inappropriate drug use was found in 13.3% of participants aged ≥65 years with RKF, 52.5% in those with eGFR 30-59 ml/min/1.73m^2, and 96% in eGFR<30ml/min/1.73m^2 over 4 years. The authors state that they may have underestimated the extent of the problem as participation rate was low and those participating were at the younger end of the age group. Analysis also highlights that they used eGFR as their kidney function estimation equation based on the Froissart et al (2005) study on the predictive performance of the MDRD and CrCl-CG equations for estimating kidney function. However, Froissart's conclusions are based on kidney disease staging and not drug dosing and they do state that CrCl-CG is more precise and accurate for age ≥65 years and low kidney function. This might also have meant that they have underestimated the problem. Kidney function estimation equations will be discussed further in the next key review area, section 2.6.

Schmidt-Mende et al (2012) in Sweden used a cross-sectional study to assess all the cases on a cardiovascular database with a diagnosis of hypertension; 3,345 older people were dispensed 27 different antihypertensive drugs in CKD stages 3-5 with over half being judged inappropriate.

Emami et al (2012) and Yap et al (2005) were also classed as 'non-local level 1, like the previous two studies, but graded 'b' as the Emami study was in a very different population, and the Yap study was retrospective which could mean there was selection bias and information bias where the exposure or outcome assessment cannot be controlled, but instead there is a need to rely on others for accurate record keeping. Emami et al randomly selected 142 patients with an elevated SrCr; 830 drug orders were evaluated and 23.2% were found to need dose adjustment. Yap et al found 25% of patients who came to an ambulatory care clinic with CrCl <50 ml/min were prescribed inappropriately high doses.

Khanal et al (2015) used a retrospective survey design to find that 28.1% of 4,035 Australians aged ≥65 years had inappropriate dosing of 31 different drugs. As only 25% of the original 30,898 cases reviewed had a documented kidney function, three quarters of the population could not be included in the survey, even though they may also be taking the relevant drugs.

In Canada older people with RKF prescribed antibiotics had excess dosing in 64%, and nitrofurantoin had been prescribed 169 times when contra-indicated in the 1,464 prescriptions studied in the prospective cohort study (Farag et al, 2014). This study was designed as a case-series to look at whether the introduction of eGFR reporting

had made a difference to prescribing in RKF. Case-series lack a comparator group and so can mean that intervening variables may not be recognised and the internal validity is compromised (Polgar and Thomas, 2013). In this study there was no difference seen before and after eGFR reporting, and here the prevalence figures are used. Also designed as a case-series was a retrospective assessment of patients with CKD in Italy which found 49.8% received at least one prescription for a nephrotoxic drug, and that 35.6% had taken NSAIDs for longer than 3 months (Ingrasciotta et al, 2014).

2.5.5.7 Prevalence outcomes: evidence from a hospital setting

Two studies were UK based so were classified as higher level evidence as they were local, but the hospital setting might mean they are not as relevant to primary care. Wong (1998) reported a prospective cohort note review of discharges from an elderly care ward in Oxford over three years and found that 25% had inappropriate drug prescribing based on their kidney function. A much more recent study retrospectively analysed case records from consecutive patients aged over 70 years medically admitted to a Hull hospital (UK) (Jones and Bhandari, 2013). They showed 56 of 100 consecutive records had one or more potentially inappropriate medication prescribed during the acute admission period, and 81 out of the 622 medications prescribed were 'inappropriate' with antibiotics and anti-hypertensives accounting for the majority.

In studies from many countries the non-compliance rates with recommendations for prescribing in RKF in the hospital setting ranged from 17% to 82.9% (Table 9). Salomon et al (2003) reviewed 886 hospital prescriptions and found 34% were inappropriate, 14% contra-indicated and 20% with inappropriate dosage given the patient's kidney function. In 2009 they went on to assess medical residents' prescribing behaviour in RKF through a simulated clinical setting where 62% of residents wrote an inappropriate order for gentamicin, 42% for diclofenac, 52% for enalapril and 28% under-dosed amlodipine. Sheen et al (2007) was a retrospective interrogation and the largest study found. They also found drug over-dosing was common in hospital patients with reduced kidney function having analysed four years of prescriptions totalling 21,768; 28% of those with moderate to severe RKF had excessive doses. Hu et al (2001) and Drenth van Maanen et al (2015) were the other larger studies found. Hu et al looked at antibiotic use for 1,044 patients aged over 80 years in a retrospective chart review. Dosing errors were found for all the antibiotics surveyed and the overall error rate was 34%. Drenth van Maanen et al was the largest prospective study and so may have fewer potential sources of bias and confounding.

They looked at the discharge medication for 1,327 participants and found 46% did not follow prescribing recommendations, and 71% of those were felt to have the potential to cause moderate to severe harm.

2.5.5.8 Drugs implicated

Very many different drugs were found to be prescribed where the kidney function was too low in the studies found. In primary care, Breton et al (2011) reported contra-indicated drugs were mainly antidiabetic agents and antihistamines, with 29 different classes of drug reported. The main classes of drugs implicated in the Level 1 primary care studies were:

- ACEIs and ARBs (Breton et al, 2011; Khanal et al, 2015; Schmidt-Mende et al, 2012).
- Antidiabetic drugs including metformin and gliptins (Breton et al, 2011; Khanal et al, 2015; Emami et al, 2012).
- Bisphosphonates (Breton et al, 2011; Khanal et al, 2015).
- Lipid-lowering drugs (Breton et al, 2011; Khanal et al, 2015).

Other drugs frequently mentioned were other antihypertensives, analgesics and digoxin.

In the UK hospital studies, similar drugs were implicated, but antibiotics were the highest reported drug class, reflecting both the high acute use in hospital, and that the primary care study designs focussed on repeat medication (Jones and Bhandari, 2013).

2.5.6 Summary

No UK primary care studies were found that would corroborate the case-note review findings from Chapter 1 to show the extent to which older people are on drugs and doses not recommended in RKF. However, evidence from primary care in other countries, where the populations are likely to be similar to the UK, has shown that prescribing for patients with reduced kidney function does not always follow the recommendations. The Breton et al (2011) French primary care large prospective cohort study found 13.3% of older people were exposed to the risk of inappropriate drug use, and 52.5% where eGFR was 30-59 ml/min/1.73m^2, giving a good indication that there was likely to be inappropriate prescribing in reduced kidney function in a wider primary care UK population, and that it should be investigated in the UK. Older people were highlighted as a particular group where prevalence of inappropriate prescribing in RKF is higher.

2.6 Key review area 2 – evidence on kidney function estimation for older people

2.6.1 Research question for key review area 2

How should kidney function be estimated when prescribing for older people?

2.6.2 Identification of relevant studies - search criteria

The UK national guidelines and resources now recommend use of 'eGFR' for kidney function estimation and disease staging, so first the relevant guidelines were reviewed for any recommendations on prescribing drugs in RKF and whether there is any assessment in relation to use for older people.

The literature was then searched to identify relevant studies. The search categories were 'Kidney function Equations/diagnostic tests' AND 'Elderly' AND 'Renal impairment' AND 'English language' (see Appendix 3, 0, for the subject headings and key words for each search category). The search term 'review' was added to the Medline search to highlight any relevant review papers.

2.6.3 Study selection – inclusion/exclusion criteria

Study selection from the search results were based on the following criteria. Although the research question is focussed on prescribing for older people, studies were included that compared kidney function estimation for drug dosing without an age limitation, as many older people have RKF and would be affected.

Inclusion

- English language.
- Primary empirical research and reviews of primary empirical research.
- Comparison of kidney function estimation equations for drug dosing.
- Comparison of kidney function estimation equations for prescribing for the older patient.

Exclusion

- Opinion or discussion articles.
- Comparison of equations for CKD, research or any other reason other than prescribing.

2.6.4 Hierarchy of evidence and appraisal

The OCEBM Levels of Evidence (2011) question 'is the monitoring test accurate' fits best with the Key review area 2 aim to assess which kidney function estimation should

be used to inform prescribing decisions. The 'Level 1' evidence, which would give greatest confidence in the findings, would therefore be 'Systematic review of cross-sectional studies with consistently applied reference standard and blinding'. Table 10 lists the hierarchy of evidence developed for key review area 2 based on the OCEBM Levels of Evidence. A grade 'b' has been added where the level may be reduced from the ideal, for example where a systematic review has not clarified or considered blinding.

As this search was looking for evidence to compare equations for prescribing, studies looking at patient outcomes would be the best test of whether an equation for estimating kidney function was effective. Studies on outcomes were searched for initially but, as this was a scoping review, the search criteria were left open to capture all relevant studies to give an overview of the evidence on kidney function estimation equations when prescribing for older people.

hierarchy of evidence	description
Level 1	Systematic review of cross-sectional studies with consistently applied reference standard and blinding
Level 1b	Systematic review of cross-sectional studies with consistently applied reference standard but blinding not considered
Level 1c	Systematic review but use of mathematical calculation for comparison rather than in-vivo study
Level 1d	Narrative review, unclear method of study selection
Level 2	Individual cross-sectional studies with consistently applied reference standard and blinding
Level 2b	Individual descriptive studies with consistently applied reference standard (clinical outcomes) to compare equations
Level 2c	Individual descriptive studies with consistently applied reference standard (drug blood levels) to compare equations
Level 2d	Individual descriptive studies with consistently applied reference standard (drug effect marker) to compare equations
Level 2e	Individual descriptive studies with consistently applied reference standard (kidney function marker) to compare equations
Level 3	Non-consecutive studies, or studies without consistently applied reference standards
Level 4	Case-control studies, or poor or non-independent reference standard
Level 5	Mechanism-based reasoning

Table 10: Hierarchy of evidence table for key review area 2 'is the monitoring test accurate?' to inform prescribing decisions, developed from the OCEBM Levels of Evidence.

The issues considered when appraising the report of a cross-sectional study were whether the results of the study were valid, what were the results, and would the results help locally in UK primary care? To aid the quality assessment the 'Critical Appraisal of a Survey' tool from the Centre for Evidence Based Management was used. For other study designs, the CASP 'Study checklists' informed the review. Studies were assessed and only included where the focus, methods, recruitment and

sampling, valid and reliable objective measurements used, and outcomes were clearly defined, relevant and appropriate to the research question.

2.6.5 Collation and appraisal

2.6.5.1 UK national guidelines

Since 2005 when the first CKD guidelines were published (Joint Specialty Committee for Renal disease of the Royal College of Physicians of London and the Renal Association, 2005), and continued in the most recent NICE CKD guideline (NICE CG182, 2014), it is recommended that kidney function is estimated using eGFR calculated using the MDRD equation. The eGFR is now reported by pathology laboratories in the UK, making it a readily available estimate of kidney function. However, as discussed in Chapter 1 (1.2.3.1) the pharmaceutical companies have historically used creatinine clearance as calculated using the Cockcroft Gault equation for their dosing recommendations in the SPCs. The UK Renal Pharmacy Group in 2006 stated that Cockcroft Gault should remain the gold standard when adjusting drug doses to an individual's kidney function; eGFR should not be used to adjust drug doses (Devaney et al, 2006).

The NICE guidelines do not discuss use of eGFR for prescribing, or specifically in the older population. The Scottish Intercollegiate Guidelines Network (SIGN) CKD guidelines (2008) discuss the fact that only 3 out of 14 studies cited found that CrCl-CG was more accurate, but that these studies looked at older patients; they also state that the MDRD equation is not validated for older people.

The BNF quotes the levels of kidney function for drug prescribing as 'eGFR' but the figures are those from the drug companies that have used Cockcroft Gault creatinine clearance.

International and national guidelines for prescribing in RKF will be discussed further in section 0.

2.6.5.2 Description of studies

Forty-one relevant studies were found from the database searches (Figure 9) investigating how kidney function should be estimated when prescribing, particularly for older people. Table 11 lists the included studies in order of the level of evidence they provide.

Until eGFR was introduced in the early 2000's CrCl-CG was the only kidney function estimate used, so all the studies found were published no earlier than 2004 when the questions first started to be raised about whether the new equation was appropriate for

drug dosing. Over half the studies found were published in the last 5 years suggesting an increased awareness and questioning of the issues.
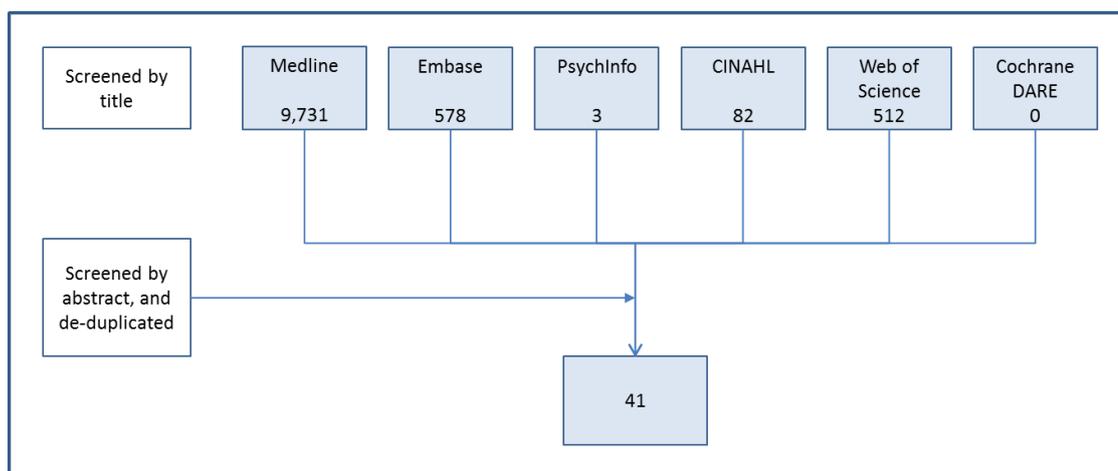
Figure 9: Number of studies identified for key review area 2.

The studies found were from a wide spread of countries, although most were from the USA (21) where eGFR was first introduced. Fifteen of the studies were from Europe, 3 of which were UK based. There is much discussion in the literature on the different creatinine assay methods and the effects that might have on the equation use and accuracy. This might mean that it is difficult to compare studies from different countries, however, if there is good evidence from many different countries, it lends confidence in the generalisability of the findings.

Nearly half the studies included focussed specifically on the effect for older people, although the age thresholds varied with ≥65/ 70/ 75/ 80 years being used.

2.6.5.3   Heterogeneity

Studies included showed wide variation in study design, kidney function measurement, estimation and analysis, which equations investigated, what drugs or reference markers, and different healthcare settings. There was also a lack of consistency in the reporting of outcome measures. As a consequence, it is inappropriate to make direct comparisons, or pool data, but by grouping according to outcome measures it has allowed independent comparison. The outcomes for the kidney function equation review are ordered in relation to level of evidence in comparing equations.

principal author	hierarchy of evidence (based on OCEBM)	year	country	study type	setting	participant number	drugs/ reference studied	outcomes
Hellou	Level 1b	2010	France	literature review		27 studies		CG was safer and less biased than MDRD in an older population in the 1 most relevant study found (Lamb et al, 2005).
Spruill	Level 1c	2008	USA	literature review		28 studies		There are substantial mathematical differences inherent in the prediction equations that make any clinical comparison difficult; the decline in kidney function with age is expressed linearly with CG and exponentially with MDRD.
Hudson	Level 1d	2011	USA	literature review		10 studies		Substantial discrepancies exist in estimates of kidney function in the elderly, and that dosing regimens for most currently available drugs are based on pharmacokinetic studies that use creatinine clearance.
Nyman	Level 1d	2011	USA	literature review				The available evidence did not support substitution of CG with MDRD for drug dosing purposes.
Corsonello	Level 2b	2012	Italy	retrospective survey	hospital	10,442	older patients	CKD-EPI-based estimates out-performed CG, and particularly MDRD-based estimates as a predictor of ADRs with hydrosoluble drugs.
Howard	Level 2b	2013	UK	cross-sectional survey	primary care	37	older people taking nitrofurantoin	Older patients with reduced kidney function were more likely to need a follow up course of an alternative antibiotic if MDRD was used to calculate the kidney function.
Melloni	Level 2b	2008	USA	retrospective survey	hospital	46,942	Anticoagulant GP IIb/IIIa inhibitors	MDRD identified fewer patients for dose adjustment and increased the likelihood of dose-associated bleeding.
Chin	Level 2c	2013	New Zealand	retrospective pharmacokinetic analysis	hospital	240	gentamicin clearance	CG was associated with the highest percentage equation result within 30% of the reference gentamicin marker: 69%, adjusted $p<0.001$ compared with MDRD, and $p=0.001$ with CKD-EPI).
Glatard	Level 2c	2015	France	pharmacokinetic analysis	hospital	78	vancomycin clearance	The use of an equation different from that used in the original dosing studies could significantly alter predictive performance.
Roberts	Level 2c	2009	Australia & Denmark	pharmacokinetic analysis	hospital	68	gentamicin clearance	MDRD overestimated kidney function as age increased (29% and up to 69%) and CG underestimated kidney function, though this was of a smaller magnitude (10%), consistent across age.
Ryzner	Level 2c	2010	USA	retrospective pharmacokinetic analysis	hospital	55	gentamicin clearance	CG was found to have a better agreement with actual drug clearance than MDRD.
Dufour	Level 2d	2012	France	prospective survey	hospital	92	enoxaparin	CG equation was able to predict the risk of higher anti-Xa levels, whilst MDRD did not
Chauvelier	Level 2e	2012	France	prospective cohort	hospital	157	measured creatinine clearance	CG gave a better prediction for measured creatinine clearance than MDRD, the result within 30% of the reference were 63% for CG and 37% for MDRD.
Dowling	Level 2e	2013	USA	cross-sectional survey	primary care	269	measured creatinine clearance	MDRD and CKD-EPI equations significantly overestimated measured creatinine clearance in elderly individuals which would lead to dose calculation errors for many drugs.
Pequinot	Level 2e	2009	France	prospective cohort	hospital	121	measured creatinine clearance	CG slightly underestimates creatinine cleaerance, and MDRD strongly overestimates it. CG gave a better prediction of measured creatinine clearance than MDRD
Rimon	Level 2e	2004	Israel	prospective cohort	hospital	154	measured creatinine clearance	Found no equations to be accurate.
Stevens	Level 2e	2009	USA	pharmacokinetic analysis		5,504	iodine-125–iothalamate urinary clearance	Conclude that MDRD can be used for pharmacokinetic studies and drug dosage adjustments.
Denetclaw	Level 4	2011	USA	case report	hospital	2	taking dofetilde	For an 83 year old woman, and a 92 year old man, calculations with MDRD caused significant increases in the QTc interval, indicating an adverse effect on the heart.
Cabello-Muriel	Level 5	2015	Spain	cross-sectional survey	hospital	222	nephrotoxic drugs	145 (65%) dose would have been different (CG lower).

Corsonello	Level 5	2011	Italy	survey	nursing home hospital	177 NH 439 hosp	general	CG different to MDRD/CKD-EPI in up to a 1/3 of patients.
Daniel	Level 5	2011	USA	retrospective survey	hospital	495	general	CG most appropriate for drug dosing.
Dowling	Level 5	2009	USA	correspondance				Using iodine-125–iothalamate urinary clearance as a reference inherently favours MDRD as that was what was used to derive the equation.
Farnier	Level 5	2013	USA	prospective survey	hospital	249	general	Use of MDRD or CKD-EPI would give an overdose in 20-25% of older patients.
Gill	Level 5	2007	Canada	cross-sectional survey	care home	180	digoxin and amantadine	MDRD 20% fewer patients would have qualified for a dose reduction.
Golik	Level 5	2008	USA	prospective survey	hospital	207	general	A significant difference in drug dosing regimens between the MDRD method and the Cockcroft Gault method.
Hanlon	Level 5	2011	USA	longitudinal survey	nursing home	1,304	general	11.89% patients via CG and only 5.98% via MDRD had evidence of potentially inappropriate prescribing of at least 1 renally cleared medication.
Helldén	Level 5	2013	Sweden	retrospective survey	primary care	790	dabigatrin, gabapentin,valaciclovir	MDRD would result in higher doses.
Hermsen	Level 5	2009	USA	retrospective survey	hospital	372	antimicrobials	40% would get different doses.
Huang	Level 5	2014	USA	cross-sectional survey	hospital	356	metformin	MDRD higher odds of inappropriate dose.
Hudson	Level 5	2014	USA	retrospective survey	hospital	4,160	allopurinol, enoxaparin, gabapentin, piperacillin/ tazobactam and sulfamethoxazole/trimethoprim	MDRD and CKD-EPI give higher KF estimates than CG.
Laroche	Level 5	2006	France	retrospective suvey	hospital & primary care	2,765	general	Clearance values higher with MDRD.
Lessard	Level 5	2013	USA	retrospective survey	primary care		general	Only 59.6% of patients would have been recommended the same dose.
McCallum	Level 5	2013	UK	cross-sectional survey	primary care	4,120	NOACs	MDRD would mean many elderly patients with AF would either incorrectly become eligible for a NOAC or would receive too high a dose.
Moranville	Level 5	2009	Italy	retrospective survey	hospital	4,698	general	Total dosing errors for MDRD ranged from 9.8% to 18.2%, depending on the medication (p < 0.01).
Norris	Level 5	2009	Canada	retrospective survey	care home	538	oseltamivir	MDRD would have meant no dose changes.
Nyman	Level 5	2015	USA	prospective cohort	hospital	6,881	general	Clinically and statistically significant differences in estimated GFR were found for CKD-EPI versus CG.
Park	Level 5	2012	USA	cross-sectional	FDA	36 drugs	multiple	Using MDRD in place of CG for dosage modification yielded higher dosing recommendations.
Roblin	Level 5	2009	France	prospective cohort	hospital	140	general	CG was 61 mL/min vs. 78 ml/min/1.73 m^2 for MDRD (p<0.0001).
Wargo	Level 5	2006	USA	survey	hospital	409	antimicrobials	Different doses in 21-37% of patients.
Wargo	Level 5	2010	USA	survey	hospital	409	antimicrobials	A discordance rate of 15-25%.
Wood	Level 5	2011	UK	cross-sectional survey	primary care	594	≥65 years	28.7% had a kidney function level of <30ml/min calculated using CrCl-CG but only 6.6% with MDRD.

Abbreviations: CrCl: creatinine clearance; CG: Cockcroft Gault; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration equation; MDRD: Modification of Diet in Renal Disease equation; NOAC: Novel oral anticoagulant.

Table 11: Studies found for scoping review area 2, listed in order of level of evidence.

2.6.5.4 Methodological quality

More than half the studies found in this search were 'mechanism-based reasoning' (Level 5, see Table 11) in that they investigated a potential risk by calculating the different kidney function estimation equations and commenting on the degree to which they differ and would alter prescribing decisions. This is useful to highlight the potential problem, particularly for older people, and has been assessed for many different drugs and healthcare settings in the 23 studies. Better quality of evidence, that would provide greater confidence in the need to change practice, would be well designed studies to show whether any difference in the equation results would affect clinical outcomes, or which equation gives a better indication on the effect of kidney function on blood levels. Thirteen studies were classified as 'Level 2':

- 3 studies looked at clinical outcomes which would give the greatest confidence in what is the best estimate to reduce the risk of harm for patients (Level 2b).
- 4 studies looked at the effect on drug levels which would be the next best indicator as a high drug level would be an increased risk of ADR (Level 2c).
- 6 made comparisons with measured creatinine or in-vitro markers which are not directly linked to risk of harm but have been shown to be an indicator (Levels 2d & 2e).

The included studies used objective and validated measurements and outcomes with analyses such as linear regression analysis and analysis of variance to investigate correlation and account for confounding factors.

No good published Level 1 systematic review evidence was found of the use of kidney function estimation for prescribing decisions.

2.6.5.5 Outcomes: Level 1 evidence - reviews

Four reviews were found that aimed to explore differences between the historically used CrCl-CG and the now widely reported eGFR for prescribing decisions, and/or use for estimating the kidney function of older people. Helou (2010) reviewed 27 studies, included if they used a gold standard glomerular filtration rate measure. This review did not assess use for prescribing, but did look at older people as a defined group. A systematic method was described, performance and bias measures discussed, but issues of blinding were not considered. The sample populations varied considerably, so they did not pool the data, but stratified to gather homogenous samples based on patient characteristics, including 'geriatrics'. Helou reported that MDRD was more precise, safe and accurate than CrCl-CG in predicting the glomerular filtration rate except in CKD patients with normal serum creatinine, where CrCl-CG was 'clearly superior'. Three studies were identified investigating the equation use in the older

patient, and one further study that allowed extraction of an older age sub-group. However, they identified weaknesses with all but one study (Lamb et al, 2005) which found that CrCl-CG was safer and less biased than MDRD in their study population (age range 69-92 years, mean 80±5). The author comments that the success of the Cockcroft Gault equation is not due to the original development study itself, which contained several weaknesses, but to its validation in several later studies compared to both measured CrCl values and reference GFR measurement methods.

Spruill et al (2008) identified 28 studies in their review to make mathematical comparisons between the equations. They discuss that there are substantial mathematical differences inherent in the prediction equations that make any clinical comparison difficult; the decline in kidney function with age is expressed linearly with CrCl-CG and exponentially with MDRD. None of the articles identified found that the use of the MDRD equation in the older person was better than the Cockcroft Gault equation for estimating renal drug elimination. The authors conclude that, although MDRD may be useful for estimating glomerular filtration rate, CrCl-CG should still be used for drug adjustments.

Two narrative reviews were found on estimating glomerular filtration rate for drug dosing, and considering older patients as a special population in this field. Both were not systematic reviews, and the method for study selection was not given. The Nephrology Practice and Research Network of the American College of Clinical Pharmacy (Nyman et al, 2011) reviewed the evidence comparing kidney function estimation equations. They concluded that the available evidence did not support substitution of CrCl-CG with MDRD for drug dosing purposes. Hudson & Nyman (2011) highlight that substantial discrepancies exist in estimates of kidney function in the elderly, and that dosing regimens for most currently available drugs are based on pharmacokinetic studies that use creatinine clearance estimated by Cockcroft Gault as the measure of kidney function.

2.6.5.6 Outcomes: use of patient based clinical outcomes to compare equations

Use of clinical outcomes to test the validity of the kidney function estimates for prescribing decisions, and for older people, would provide evidence of what actual harm might be caused. Four studies were found that investigated patient based clinical outcomes. Two were high quality, large trials. The other two were one case study report and a small single practice pilot study that give an indication of other possible differences in patient outcomes with use of the different equations.

Melloni et al (2008), surveyed patient records on a registry of those admitted for non-ST-segment elevation acute coronary syndromes, and whether the kidney function estimation equation used would inform the dosing of injected anticoagulants (glycoprotein-IIb-IIa-inhibitors e.g. eptifibitide, or low molecular weight heparins e.g. enoxaparin). There was a linear relationship between glomerular filtration rate and risk of bleeding. The sample of 46,942 patients only needed 5.5% to be excluded for the final analysis because of key variables not being available (such as SrCr, age, weight). Objective validated measurements and outcomes were clearly defined and there was a detailed analysis of possible confounding factors such as race, diabetes, or prior myocardial infarction. Major bleeding events were more frequent in individuals who received doses of glycoprotein-IIb-IIa-inhibitors as assessed by the MDRD equation versus CrCl-CG (21.8% vs 17.8%; odds ratios MDRD 1.57 [95%CI: 1.35-1.84], CrCl-CG 1.31 [95%CI: 1.12-1.54]). MDRD identified fewer patients for dose adjustment and increased the likelihood of dose-associated bleeding. From a safety perspective, the authors state that their results support current recommendations for use of the CrCl-CG formula for antithrombotic dosing in an acute coronary syndrome population.

Corsonello et al (2011) surveyed data from a large collaborative observational study group 'The Italian Group of Pharmacoepidemiology in the Elderly' which periodically surveys drug consumption and occurrences of ADRs. Records for 17,186 patients, mean age 70.2 ±14.9 years, were reviewed. In this study 39% needed to be excluded because variables were not available, which is a limitation of this design. The 6,744 patients excluded were significantly older (age >80 years 40.1% vs 28.8%, p<0.001), more likely to be female, and have functional and cognitive impairment, which might impact on the results of this study. In the 10,442 hospitalised patients CKD-EPI-based estimates out-performed CrCl-CG, and particularly MDRD-based estimates as a predictor of ADRs with hydrosoluble drugs. They state that this study shows there is a difference, but that it does not prove use of any of the equations would lead to a reduction in ADRs, but that it strengthens the need for a formal trial.

Two case studies of older patients have been reported where the USA antiarrhythmic agent dofetilde dose calculations with MDRD, as opposed to CrCl-CG caused significant increases in the QTc interval, indicating an adverse effect on the heart (Denetclaw and Dowling, 2011). A small pilot audit on the effectiveness of nitrofurantoin suggested that older patients with reduced kidney function were more likely to need a follow up course of an alternative antibiotic if MDRD was used to calculate the kidney function (Howard & Wood, 2012). The records of 37 older patients who had had a course of nitrofurantoin at one GP practice were reviewed. Where CrCl

was >60ml/min, 15 were reviewed and none needed further antibiotics or had any record of still being symptomatic; for the 22 with CrCl <60ml/min 18 had further antibiotics or were recorded as still symptomatic. Only 7 of the latter group had an eGFR <60 ml/min/1.73m^2 so many would have been missed.

2.6.5.7 Outcomes: Use of drug levels to compare equations

Drug levels are used in healthcare to indicate whether effective levels have been reached, or risk of ADR if levels are too high. Use of drug levels is therefore a good indicator for comparison of kidney function estimation equations.

Gentamicin

Three studies have used gentamicin as a marker for comparison of the equations. Gentamicin is a highly water-soluble antibiotic that undergoes complete renal excretion via filtration so it is well suited as a marker of kidney function, and there is standard pharmacokinetic monitoring. Roberts et al (2009) studied the gentamicin clearance for 68 patients in 2 hospitals. They describe objective and validated measurements and outcomes with linear regression analysis and analysis of variance to investigate correlation and account for confounding factors. They found that MDRD overestimated kidney function as age increased (29% and up to 69%) and CrCl-CG underestimated kidney function, though this was of a smaller magnitude (10%), consistent across age, and thus the CrCl-CG is better suited for dose calculation, especially for older people; age significantly influenced MDRD overestimation in their population (p = 0.037).

Ryzner (2010) did a retrospective review of patients receiving aminoglycoside therapy (e.g. gentamicin). Fifty-five patients were identified on a hospital internal pharmacy database. CrCl-CG was found to have a better agreement with actual drug clearance than MDRD. The concordance correlation coefficient was 0.53 (0.18-0.88) for CrCl-CG and 0.41 (0.04-0.78) for MDRD, and this was agreed with the Pearson's coefficient (0.76 for CrCl-CG, and 0.65 for MDRD). Subgroup analysis showed highest correlations for the CrCl-CG equation was for >65 year olds, females, and African Americans.

Chin et al (2013) reviewed data for 240 patients on a gentamicin dosing database. They found that CrCl-CG was associated with the highest percentage equation result within 30% of the reference gentamicin marker: 69%, adjusted p<0.001 compared with MDRD, and p=0.001 with CKD-EPI. CKD-EPI performed better when adjusted for body surface area, but that is not done in practice. The authors state that their study adds to the evidence base for using CrCl-CG for drug dosing.

Vancomycin

The rate of elimination of vancomycin is directly related to creatinine clearance. Glatard et al (2015) compared the abilities of different kidney function estimation equations to describe vancomycin pharmacokinetics in 78 elderly patients. Their analyses showed considerable variation for the different estimation equations and they conclude that the use of an equation different from that used in the original dosing studies could significantly alter predictive performance.

2.6.5.8   Outcomes: use of a drug effect marker to compare equations

Older people have an increased risk of low molecular weight heparin accumulation leading to an increased bleeding risk from raised 'anti-Xa' levels. In 92 consecutive hospitalised patients older than 65 years receiving prophylactic enoxaparin treatment, the CrCl-CG equation was able to predict the risk of higher anti-Xa levels, whilst MDRD did not (Dufour et al, 2012). A significant correlation was observed between anti-Xa activity and glomerular filtration rate estimated with the CrCl-CG (r=0.43; p =0.0002), but no significant association between anti-Xa levels and MDRD estimated glomerular filtration rate (p=0.33) was observed.

2.6.5.9   Outcomes: use of kidney function markers to compare
equations

Comparison with measured creatinine clearance

When comparing results using kidney function estimation equations with measured creatinine clearance, 3 of the 4 studies looking at the effect in older people found that MDRD was least effective. Pequignot et al (2009) compared the MDRD and CrCl-CG formulae with 24hr urine creatinine for 121 consecutive patients aged over 70 years; they concluded that in elderly hospitalised patients, CrCl-CG slightly underestimates creatinine clearance, and MDRD strongly overestimates it. CrCl-CG gave a better prediction of measured creatinine clearance than MDRD. Dowling et al (2013) report a cross-sectional analysis of data from 269 community-dwelling volunteers (mean age 81 ±6 years) randomly selected from the Baltimore Longitudinal Study of Aging. They found the MDRD and CKD-EPI equations significantly overestimated measured creatinine clearance in elderly individuals which would lead to dose calculation errors for many drugs. Chauvelier et al (2012) conducted a prospective, cross-sectional, observational study in four hospital geriatric wards, and recruited 157 consecutive patients admitted to the wards who were aged >75 years and had an indwelling urinary catheter. They too found CrCl-CG gave a better prediction for measured creatinine clearance than MDRD, the result within 30% of the reference were 63% for CrCl-CG and 37% for MDRD. Rimon et al (2004) found no equations to be accurate in their

prospective, observational study of 154 consecutive patients aged ≥80 years with urinary catheters, admitted over a 12-month period to the acute geriatric ward, although their threshold was set at ± 10% from measured creatinine clearance which is lower than other studies.

Comparison with chemical markers

Stevens et al (2009) is frequently quoted as having the largest study population to compare drug dosing recommendations based on measured glomerular filtration rate and kidney function estimating equations. They used a pooled data set of 5,504 patients from 6 studies and 4 clinical populations, and they concluded that MDRD can be used for pharmacokinetic studies and drug dosage adjustments. However, the mean population age was 47 years and so there cannot be confidence that this finding is applicable to an older population. Comments on this study by Hudson & Nyman (2011) highlight that the reference was to measured iodine-125–iothalamate glomerular filtration rate, which is different to how drug pharmacokinetic studies are done, making comparisons less valid. Dowling et al (2009) points out that using iodine-125–iothalamate urinary clearance as a reference inherently favours MDRD as that was what was used to derive the equation.

Froissart et al (2005) used renal clearance of the marker [51]chromium edetic acid ([51]CrEDTA), which is not metabolized and is excreted solely by the kidney, to compare using either the CrCl-CG equation or the MDRD formula in a cohort of 2,095 adult Europeans. Their conclusions were based on staging kidney disease, not drug dosing, but they did state that MDRD was more precise and accurate except for women aged ≥65 years with low kidney function.

2.6.5.10 Outcomes: comparison of the effect of equation choice by calculation

The difference in dosing resulting from calculations using the different equations has been reported on in many studies. This 'mechanism-based reasoning' has been classified as 'Level 5' in the OCEBM Levels of Evidence (Oxford Centre for Evidence-Based Medicine, 2011) and the 23 studies found are listed in Table 11 as 'Level 5'. All these studies suggest that there would be a significant difference in the dose of drugs, or use of drugs, depending on whether eGFR (calculated using MDRD) or CrCl-CG has been used. The largest prospective cohort study (n=6,881) found clinically and statistically significant differences for CKD-EPI versus CrCl-CG (Nyman et al, 2015), and a retrospective study (n=4,698) found total dosing errors for MDRD ranged from 9.8% to 18.2%, depending on the medication ($p < 0.01$) (Moranville, 2009). In the case note review (Chapter 1) 28.7% had a kidney function level of <30ml/min calculated

using CrCl-CG but only 6.6% with MDRD. However, the study designs do not include any reference markers or outcomes to see if there are actually any differences on the effect of the drug for patients, or ADRs caused.

2.6.5.11 The need to use estimation equations not serum creatinine

Several studies have shown that older people can have significantly low kidney function despite a 'normal' serum creatinine level (SrCr). For example, in a prospective assessment of 2,781 people referred for a SrCr level in Canada, 91.4% were normal but for 12.6% of those aged 60-69 years CrCl was ≤50ml/min, and 47.3% of those aged 70 years and older (Duncan et al, 2001). Also in Canada, a look back at out-patients found that just 15 of the 55 people with severe renal failure had been referred to nephrology because only SrCr had been assessed (Swedko et al, 2003). Gianelli et al (2007) compared SrCr to measured CrCl and 25% of those aged ≥65 years with a normal SrCr had a measured CrCl of <60ml/min, and Malyszko et al (2011) found that those aged ≥65 years had a significantly lower kidney function compared to younger people despite identical SrCr.

2.6.5.12 Drugs implicated

The range of studies found highlight that prescribing decisions for many drugs would be affected by which equation is used; examples include gabapentin, antibiotics, and anticoagulants (Hudson and Nyman, 2011; Melloni et al, 2008; McCallum et al, 2013).

2.6.6 Summary

Only two good quality outcome studies were found that would give the most valid measure of effect for patients, and they were for specific drugs only. However, drug blood level studies, and chemical marker studies, using different drugs and methods, show that the Cockcroft Gault calculation should still be used for drug dosing decisions and, in particular for the older patient because the MDRD equation is likely to overestimate the kidney function level. The theoretical calculation studies suggest that a wide range of drugs would be affected by the choice of estimation equation used for prescribing decisions.

2.7 Key review area 3 – evidence on the risks of prescribing in reduced kidney function

2.7.1 Research question for key review area 3

What are the risks to the older person in primary care of not following the recommendations for prescribing in reduced kidney function?

2.7.2 Identification of relevant studies- search criteria

The search categories were 'Renal impairment' AND 'ADRs' AND 'Elderly' AND 'Primary Care' (see Appendix 3, 0, for the subject headings and key words for each search category). The search term 'review' was added to the Medline search to find any relevant review papers.

2.7.3 Study selection – inclusion/exclusion criteria

Study selection from the search results were based on the following criteria. Although the research question is focussed on primary care, other healthcare settings were included for comparison.

Inclusion

- English language.
- Primary empirical research and reviews of primary empirical research.
- Intervention or outcome relating to assessment risks associated with not applying the prescribing recommendations in reduced kidney function.

Exclusion

- Opinion or discussion articles.

2.7.4 Hierarchy of evidence and appraisal

The research question asked 'what are the risks of treatment harm?' As the potential risk of harm is from drugs with a known ADR profile, the enquiry is 'how common is the problem' of ADRs when kidney function is not taken into account'. The OCEBM Levels of Evidence (2011) would then give the 'Level 1' evidence to be 'local and current random sample surveys (or censuses)', where, for example, an ADR has caused a hospital admission. Some ADR effects may need to be studied over time, for example mortality, where a longitudinal study would be required. If good level 1 evidence is not found then studies of lower level relevance, and non-local evidence, would give an insight into whether further research is needed. Table 12 lists the hierarchy of evidence developed for key review area 3 based on the OCEBM Levels of Evidence.

The issues considered when appraising the report of a descriptive survey were whether the results of the study were valid, what were the results, and would the results help locally, i.e. in UK primary care. To aid the quality assessment the 'Critical Appraisal of a Survey' tool from the Centre for Evidence Based Management was used. For other study designs, the CASP 'Study checklists' informed the review. Studies were assessed and only included where the focus, methods, recruitment and sampling, valid and reliable objective measurements used, and outcomes were clearly defined, relevant and appropriate to the research question.

hierarchy of evidence	description
Level 1	Local and current random sample surveys (or censuses)
Level1b	Local random sample surveys (or censuses) - not current/ not primary care
Level 2	Systematic review of surveys that allow matching to local circumstances
Level 2b	Systematic review of surveys that allow matching to local circumstances - not current/ low quality for primary care
Level 3	Local non-random sample
Level 4	Local case series
Non-local level 1	Non-local and current random sample surveys (or censuses)
Non-local level 1b	Non-local random sample surveys (or censuses) - not current/ not primary care
Non-local level 3	Non-local non-random sample
Non-local level 3b	Non-local non-random sample - not current/ not primary care/ very different population
Non-local level 4	Non-local case series
Non-local level 4b	Non-local case series - not current/ not primary care

Table 12: Hierarchy of evidence table for key review area 3 'how common is the problem?' developed from the OCEBM Levels of Evidence.

As this search was looking for evidence of the risks of not following the prescribing recommendations for RKF, a prospective investigation would give more precise estimates of the relative risk of the outcome based on exposure, and have fewer potential sources of bias and confounding than retrospective studies. However, where a risk might be small, the large numbers needed might require a retrospective design to make it feasible. The search criteria were left open to capture all relevant studies.

2.7.5 Collation and appraisal

2.7.5.1 Description of studies

Thirty-two relevant papers were found from the database searches (Figure 10) on the risks to patients if prescribing in reduced kidney function does not follow the recommendations. Table 13 lists the included studies in order of the level of evidence they provide.

ADRs resulting from inappropriate prescribing in RKF seems to have been recognised in the literature from the 1990s, with studies found dating from that time. Most of the

studies found come from the early 2000s onwards suggesting an increased awareness and enquiry into the risks of drugs when kidney function is reduced.

Screened by title	Medline 5,083	Embase 10,696	PsychInfo 28	CINAHL 1,261	Web of Science 394	Cochrane DARE 0
Screened by abstract, and de-duplicated						
			32			
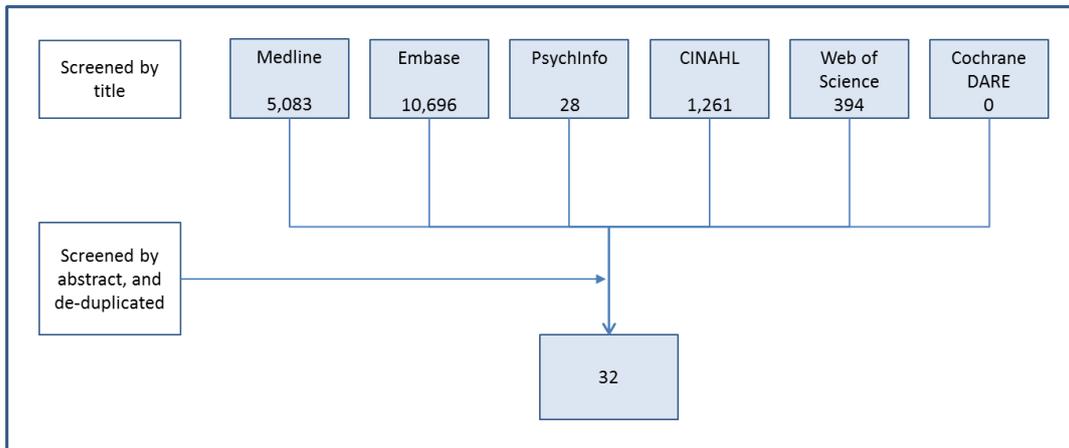
Figure 10: Number of studies identified for key review area 3

The OCEBM Levels of Evidence state that local evidence is best to understand how common a problem might be (Oxford Centre for Evidence-Based Medicine, 2011), but only three studies were identified from the UK, and all were drug specific (NSAIDs, heparin, and nitrofurantoin). There were no geographical limits put on the scoping review searches and most studies were based in countries that might be considered to have similar populations to the UK, although the healthcare systems may be different, for example the USA (x7), Australia (x2), and Western Europe (x13) (see Table 13). Seven studies were from differing populations, and were all hospital based, Taiwan (Chen et al, 2014), Israel (Zaidenstein et al, 2002), India (Cestalino et al, 2011; Joshua et al, 2007), Malaysia (Hassan et al, 2011), and 2 from Dubai (both Sharif-Askari et al, 2014). These studies, that report a wide range of ADRs related to prescribing in RKF, suggest it should be recognised as a multi-national problem.

Only six studies found were based in primary care, one in the UK. Three further studies looked at ADRs on admission which were most likely to have originated in primary care, one of which was UK based focussing on NSAIDs as a cause of hospitalisation (Evans et al, 1995). The prescribing systems and procedures are different to those in hospitals, including advanced computerised patient record systems used in UK primary care that might mean different findings to hospital based studies.

principal author	hierarchy of evidence (based on OCEBM)	year	country	study type	setting	participant number	participant type	outcomes
Evans	Level 1b	1995	UK	case control	hospital admission	207	admission with AKI	Recent exposure to NSAIDs and previous exposure to aspirin were independently associated with hospitalisation for AKI.
Marcum	Level 2b	2011	USA	narrative literature review			anti-hypertensives	The most common ADRs associated with antihypertensive use in CKD include hyperkalemia, AKI, and orthostatic hypotension.
Howard	Level 3	2013	UK	cross-sectional survey	primary care	37	older people taking nitrofurantoin	Older patients with reduced kidney function were more likely to need a follow up course of an alternative antibiotic if they had RKF and nitrofurantoin was prescribed.
Farooq	Level 3	2004	UK	case-note review	hospital	10	on heparin	8% ADR rate found related to use of drugs in RKF
Breton	Non-local Level 1	2011	France	prospective cohort	primary care	8,701	≥65 years	Mortality increased by 40% for older people on drugs inappropriate for level of kidney funciton.
Borchelt	Non-local Level 1	1994	Germany	cross-sectional survey	primary care	336	≥70 years	25.8% had a definite and specific ADR, related to kidney function.
Adams	Non-local Level 1	2011	Australia	longitudinal survey	primary care	357	general population	30.8% on NSAIDs had Stage 3 or higher CKD.
Helldén	Non-local Level 1	2009	Sweden	retrospective survey	hospital admission	154	≥65 years	14% of hospital admissions were primarily caused by ADRs and one-third of these were related to impaired kidney function.
Geerts	Non-local Level 1	2013	Netherlands	retrospective cohort	primary care	21,317	had a course of nitrofurantoin	Risk of pulmonary adverse events leading to hospitalisation was significantly increased (HR 4.1, 95 % CI 1.31-13.09).
Handler	Non-local Level 1	2014	USA	retrospective survey	nursing home	249	nursing home resident with AKI alert	AKI alerts for 249 patients still led to 70 cases of kidney injury and 44 cases of failure
Chen	Non-local Level 1b	2014	Taiwan	case control	hospital	295	≥65 years	Increased concentration of serum creatinine was an independent risk factor for an ADR caused hospital admission.
Caamano	Non-local Level 1b	2005	Italy	cross-sectional survey	hospital	19,070	≥65 years registered for home care	RKF is associated with ADR at hospital admission (odds ratio [OR] = 1.76; 95% CI: 1.41–2.55).
O'Connor	Non-local Level 1b	2012	Ireland	prospective	hospital	513	>65 years	26% of 513 had an ADR, and RKF increased the risk of ADR
Leendertse	Non-local Level 1b	2012	Netherlands	prospective case-control	hospital	714	medication-related admission	10% of admissions were considered to be related to renal impairment.
Blix	Non-local Level 1b	2006	Norway	prospective survey	hospital	201	eGFR<60 ml/min/1.73m^2	62% had drug realted problems linked with renal risk drugs, and 26% of the renal risk drugs were associated with DRPs.
Cestac	Non-local Level 1b	2003	France	prospective survey	hospital	334	on heparin	10.5% ADR rate found related to use of drugs in RKF

Henry	Non-local Level 1b	1997	Australia	retrospective survey	hospital admission	110	acute admission with raised SrCr	Association found between consumption of NSAIDs and the development of functional renal impairment.
Melloni	Non-local Level 1b	2008	USA	retrospective survey	hospital	46942	Anticoagulant GP IIb/IIIa inhibitors	There was an increased risk of bleeding.
Corsonello	Non-local Level 1b	2012	Italy	retrospective survey	hospital	10442	older patients	Increased ADRs with hydrosoluble drugs.
Corsonello	Non-local Level 1b	2005	Italy	retrospective cohort	hospital	11,687	≥65 years	Both concealed and overt renal failure were associated with ADR to hydro-soluble drugs.
Corsonello (2)	Non-local Level 1b	2005	Italy	retrospective cohort	hospital	2,257	diabetic patients	Both concealed and overt renal failure were associated with ADR to hydro-soluble drugs.
Zaidenstein	Non-local Level 3b	2002	Israel	prospective survey	hospital	496	on CVD drug	Higher urea levels (RKF) associated with ADRs
Castelino	Non-local Level 3b	2011	India	prospective cohort	hospital	308	RKF	19% had an ADR on a nephrology ward
Hassan	Non-local Level 3b	2011	Malaysia	prospective cohort	hospital	300	CKD	44% ADRs, 22.7% suspected as the cause for admission, and 21.3% happened during admission
Hug	Non-local Level 3b	2009	USA	prospective cohort	hospital	900	reduced CrCl	10% ADR rate found related to use of drugs in RKF
Schuler	Non-local Level 3b	2008	Austria	prospective cohort	hospital	543	≥75 years	17.8% ADR rate found related to use of drugs in RKF
Sharif-Askari	Non-local Level 3b	2014	Dubai	prospective cohort	hospital	512	stage 3-5 CKD	12.1% ADR rate found related to use of drugs in RKF
Sharif-Askari	Non-local Level 3b	2014	Dubai	prospective cohort	hospital	488	unfractionated heparin or enoxaparin	Major bleeding occurred in a third of CKD patients who received enoxaparin or heparin
Joshua	Non-local Level 3b	2007	India	retrospective survey	hospital	244	ADR on a nephrology ward	17% ADR rate found related to use of drugs in RKF
Fischer	Non-local Level 3b	2013	USA	retrospective cohort	hospital	7,413	Acute coronary syndrome on clopidogrel	Significantly higher risk of death and an over 2 fold increase in major bleeding in eGFR <60 ml/min/1.73m^2
Denetclaw	Non-local level 4b	2011	USA	case report	hospital	2	taking dofetilde	For an 83 year old woman, and a 92 year old man, calculations with MDRD caused significant increases in the QTc interval, indicating an adverse effect on the heart.
Lazarou	Not classified	1998	USA	narrative literature review				kidney function was a factor rarely reported in the studies sampled and so they could not determine the effect on ADR rate

Abbreviations: ADR: adverse drug reaction; AKI: acute kidney injury; CKD: chronic kidney disease; DRP: drug related problem; MDRD: Modification of Diet in Renal Disease equation; NOAC: Novel oral anticoagulant; NSAID: non-steroidal anti-inflammatory; RKF: reduced kidney function; SrCr: serum creatinine.

Table 13: Studies found for scoping review area 3, listed in order of level of evidence.

The research question was to focus on older people, and 9 of the studies had older participants only. Other studies were included as many discussed that older people are more likely to have reduced kidney function; also, many studies reported older mean ages.

2.7.5.2   Heterogeneity

The included studies showed considerable variation in the characteristics of healthcare settings, patients versus drugs analysed, age thresholds, and kidney function measurement and estimation differences, similarly as discussed in previous sections.

How renal risk drugs were defined and recognised also varied considerably, with different reference sources quoted, although many mentioned the BNF as well as their local reference sources. Some studies looked at ADRs from all drugs affected by RKF, whilst some focussed specifically on one drug or drug class, e.g. NSAIDs or anticoagulants.

Definition, recognition and measurement of ADRs and their frequency were also widely varied. Nine studies describe using the World Health Organisation (WHO) definition of ADR as 'a noxious, unintended, and undesired effect of a drug, which occurs at doses in humans for prophylaxis, diagnosis, or therapy' (World Health Organisation, 1966). 'Adverse drug event' (ADE) is used in 7 studies which is 'an injury resulting from administering a drug' (Bates et al, 1993); this includes errors of administration, although that would not be relevant for this review. One study used 'drug-related-problem' defined by the Pharmaceutical Care Network Europe (2002) as 'an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes', which differs by including potential adverse effect. Another study use 'medication related problem' (MRP) which is a standardised classification by Strand et al (1990).

As a consequence of the wide variation, it is inappropriate to make direct comparisons for the whole set of included studies, or pool data. The studies were therefore grouped by healthcare setting to allow comparison, and then further organised into ADR type, for example, mortality, general ADR rate, NSAIDs, and anticoagulants.

2.7.5.3   Methodological quality

Use of the OCEBM hierarchy of evidence levels, and CEBM/CASP appraisal checklists, reveal only 4 of the studies would be classified as there were just 3 'local 'UK studies found, and 1 review (Table 13). The review had no method reported and was specific to ADRs associated with antihypertensives among older adults with chronic kidney disease. The 3 UK studies had a narrow drug focus and so, again,

would not provide generalisable evidence. However, the evidence from other countries was classified as 'non-local' but 'Level 1' in 6 studies, and 'Level 1b' in 11 studies, mostly where they were hospital based rather than primary care. A further 9 studies were given a level of 'Non-local level 3' where the study population was less likely to be similar to UK patients, or where it was not clear that the sampling was randomised or census.

The longitudinal studies may have attrition bias if not all patients are followed up to the end, and the retrospective studies may have missing data from selection bias and information bias where the exposure, record keeping or outcome assessment cannot be controlled.

2.7.5.4 Risk of harm outcomes: reviews

No reviews were found that looked specifically at the effect of reduced kidney function on ADR rate.

In Lazarou and Pomeranz's USA review (1998) it was reported that kidney function was a factor rarely reported in the studies sampled and so they could not determine the effect on ADR rate.

Marcum and Fried (2011) reviewed the literature to describe the potential medication errors and ADRs associated with antihypertensives among older adults with chronic kidney disease. This was a narrative review with no method provided other than 'we have reviewed the literature', consequently this was not classified as Level 1 evidence, but Level 3 at best. However, it is interesting that they state that few studies have been published describing ADEs in older adults with CKD, and that there is a paucity of clinical trial data in older adults with hypertension. They report the most common ADEs associated with antihypertensive use in this high risk population of older adults with CKD include hyperkalaemia, acute kidney injury, and orthostatic hypotension.

2.7.5.5 Risk of harm outcomes: local studies based in UK primary care

No studies were found to provide evidence of what the risks are to the older patient of not following the recommendations for prescribing in reduced kidney function in the UK primary care.

2.7.5.6 Risk of harm outcomes: primary care based studies in other countries

Mortality

The high quality French prospective cohort study in primary care by Breton et al (2011) has been discussed previously regarding its prevalence data (2.5.5.6). This longitudinal study also aimed to assess any effect on mortality for older people taking

one or more drugs inappropriate in reduced kidney function. The 6-year mortality was assessed by active follow-up of all 8,701 participants, with only 8 for whom it remained unknown. Exposure of older people (≥65 years) to inappropriate drug use in RKF was independently related to higher all-cause mortality (hazard ratio 1.4, 95% CI 1.0–1.9) in participants with eGFR <60ml/min/1.73m^2; all-cause mortality was significantly increased by 40%.

General ADR rate

Borchelt and Horgas (1994) report from the Berlin Aging Study where a representative sample of the primary care population aged 70 years and older (n=336) were screened for ADRs, fluid and electrolyte balance, and kidney function. They found 25.8% had a definite and specific ADR related to level of kidney function. Nursing home residents (mean age 74.2 years) in the USA were studied by Handler et al (2014) in a retrospective survey to determine the incidence of drug-associated acute kidney injury (AKI). They found that 668 AKI alerts for 249 patients still led to 70 cases of kidney injury and 44 cases of kidney failure. The most common medication classes included in the AKI alerts were diuretics, ACEIs/ARBs, and antibiotics.

NSAIDs

Non-steroidal anti-inflammatory drugs (NSAIDs) are a common cause of reported adverse drug side-effects including toxicity to the kidney. Adams et al (2011) analysed data from 3,206 adults attending first follow-up of the North West Adelaide Health Study in 2004-2006, a longitudinal representative population study. Objective and validated measurements were described and Pearson's Chi-square tests determined significant differences in proportions and multiple logistic regression was used to examine associations of socio-demographic characteristics with use of NSAIDs. They found that there was a high prevalence of NSAID use in Australia among groups at-risk for significant drug-related adverse events: 60.8% had hypertension, 30.8% had Stage 3 or higher chronic kidney disease, 17.2% had a history of cardiovascular disease and 20.7% had a > 15% 10-year CVD risk.

Nitrofurantoin

Geerts et al (2013) used a large retrospective cohort study to determine whether treatment with the antibiotic nitrofurantoin in women with urinary tract infection (UTI) and renal impairment in primary care is associated with a higher risk of ineffectiveness and/or serious adverse events than in women without renal impairment. The secondary outcome in the design of this study was the occurrence of serious adverse events of nitrofurantoin leading to hospitalisation within 90 days. In the cohort of 21,317 people who had taken nitrofurantoin the overall incidence density for adverse

events was 0.02 per 1,000 person-days, but in patients with renal impairment (<50 ml/min/1.73 m^2) the risk of pulmonary adverse events leading to hospitalisation was significantly increased (HR 4.1, 95 % CI 1.31-13.09). In the Howard at al (2013) pilot study discussed in Key review area 2 (1.6.5.6) older patients with RKF were more likely to need a follow up antibiotic indicating a lack of effect of nitrofurantoin and an increased risk from the infection.

2.7.5.7 Risk of harm outcomes: hospital admissions

Although these studies are based in hospital, by focussing on admissions the causes are most likely to have originated in primary care.

Older people (≥65 years) registered to receive home healthcare admitted to the emergency department of a Swedish hospital were studied by Helldén et al (2009) to look at ADR rate and whether level of kidney function was a factor. This retrospective cohort study of 154 participants found that 14% of hospital admissions were primarily caused by ADRs and one-third of these were related to impaired kidney function. Creatinine clearance was significantly lower in the group with ADRs than those without. This cohort was more likely to be admitted than the comparison group who were not registered for homecare; they were older and more fragile. This study highlights the particular importance of kidney function assessment for very elderly and frail patients to reduce hospital admission.

In a much larger cross-sectional database study, Caamaño et al (2005) aimed to identify and to measure the association between socio-demographic factors and the prevalence of adverse drug reaction at hospital admission in an elderly population in Italy. They assessed 19,070 admissions and found that 4.3% were diagnosed with an ADR and that the presence of RKF is associated with ADR at hospital admission (odds ratio [OR] = 1.76; 95% CI: 1.41–2.55). They used logistic regression to assess the effect of hepatic and renal diseases, number of diseases, number of drugs used, albumin index (indicator of nutritional condition) and cognitive function. Other factors associated with admission were number of drugs consumed (OR = 1.74; 95% CI: 1.47-2.08) and, to a lesser extent, a low nutritional status (OR = 1.39; 95% CI: 1.17-1.64).

In the Netherlands, 714 medication-related hospital admissions reported in the prospective multicentre study HARM (Hospital Admissions Related to Medication) were analysed. The patients (mean age 68 years) were divided into 3 groups based on the availability of creatinine levels: group A, the home-monitored group (n = 227); group B, the hospital-monitored group (n = 420); and group C, the unmonitored group

(n = 67). After adjustment for confounders, 70 admissions (10%) were considered to be related to renal impairment (Leendertse et al, 2012).

One study was found based in Taiwan where the population and healthcare system is likely to be different to that of the UK. It also shows that RKF can be a factor in ADRs leading to admission. This prospective case-control study used logistic regression analysis to show that increased concentration of serum creatinine was an independent risk factor in 295 ADRs in older people that led to an emergency department visit (adjusted OR=1.5; 95% CI: 1.1-2.2); diuretics, analgesics, cardiovascular agents, anti-diabetic agents and anticoagulants were the medications most commonly associated with an ADE (Chen et al, 2014).

NSAIDs

NSAIDs are frequently cited as a factor in causing hospital admission. Two case-control studies highlight that NSAIDS are an important cause of RKF and AKI. Henry et al (1997) analysed the relationship between recent use of NSAIDs and the presence of functional renal impairment present at the time of hospitalisation with a range of clinical problems. In 110 consecutive hospital admissions, with 189 controls, the association between consumption of NSAIDs (including non-prophylactic aspirin) and the development of functional renal impairment, adjusted OR, was 6.6 (0.75, 57.8) in subjects with a previous history of renal disease.

A UK case-control study of patients hospitalised with AKI showed that recent exposure to NSAIDs and previous exposure to aspirin were independently associated with hospitalisation for AKI, with adjusted odds ratios of 2.20 (1.49-3.25) and 2.19 (1.46-3.30), respectively (Evans et al, 1995). There is an approximate doubling of the risk of hospitalisation with AKI with use of oral NSAIDs.

2.7.5.8   Risk of harm outcomes: studies based in hospital

ADR rate

ADR rates relating to RKF ranged from 3% to 62% in the fourteen hospital based studies found. The largest is an earlier retrospective study of the hospital data from the 'Italian Group of Pharmacoepidemiology in the Elderly' (GIFA) collaborative observational study group to that discussed in 1.6.5.6 on risk of ADRs in RKF and which equation would be a better predictor (Corsonello et al, 2012). Analysis of 11,687 older people (>65 years) consecutively admitted to the participating centres revealed that 8% had an ADR during their hospital stay, and a third of those were from hydro-soluble drugs (Corsonello et al, 2005). The 3 categories studied were grouped according to creatinine level and eGFR. After adjusting for potential confounders, both

concealed (OR, 1.61; 95% CI, 1.15-1.25) and overt (OR, 2.02; 95% CI, 1.54-2.65) renal failure were associated with ADR to hydro-soluble drugs. 'Concealed' renal failure was defined as renal insufficiency despite a normal serum creatinine, as is more likely for older people because of loss of muscle mass (and consequently lower production of creatinine). As has been highlighted for many other studies, 5,499 (32%) of the patients had been excluded, most of whom because a kidney function estimation was not available, although they were analysed to show that the excluded patients did not differ otherwise from the study population. The authors found similar results when they studied 2,257 older diabetics, where RKF is highly prevalent, from the same GIFA study group where 10% had an ADR during their hospital stay, and 42% of those were to hydrosoluble drugs (Corsonello et al (2), 2005). Multivariable Cox regression analysis showed that both concealed (hazard ratio = 1.90; 95% confidence interval, 1.04-3.48; p =.036) and overt (hazard ratio = 2.23; 95% confidence interval, 1.40-3.55; p =.001) renal failure were significantly associated with ADR to hydrosoluble drugs.

In the prospective multi-centre design used by Blix et al (2006), fewer participants were enrolled (827), but only 2.3% needed to be excluded because of kidney function data not being available, a strength of this design. 'Drug related problems' (DRPs) linked to the renal risk drugs were found for 62% of the patients with eGFR <60ml/min/1.73m^2, and 26% of the renal risk drugs were associated with DRPs. The most common drug classes associated with DRPs were antibacterials, antithrombotic agents, angiotensin-converting enzyme (ACE) inhibitors, opioids and non-steroidal anti-inflammatory drugs (NSAIDs).

O'Connor et al (2102) prospectively studied 513 acutely ill patients aged >65 years in a hospital in Ireland; 26% of 513 had an ADR, and RKF increased the risk of ADR (OR: 1.81, 95% CI: 1.12-2.92). Schuler et al (2008) studied hospital patients aged 75 years and older and found ADEs for 17.8%, half of which had caused the admission to hospital; renal dysfunction was one of the risk factors found for ADE. In the 90 ADEs found in 900 USA community hospital patients with RKF exposed to nephrotoxic drugs, 51% were serious, 4.6% life-threatening and 91% were judged preventable; this report had a minimal description of the method used, but a comprehensive presentation of results (Hug, 2009).

Five further studies were found from countries that are likely to have a very different population, but they have been included to compare whether ADRs from renally excreted drugs are a problem in other parts of the world. A retrospective study of inpatients with ADRs (July 2005-June 2006) in a nephrology ward in India found that of

1,464 case records reviewed, 267 drugs contributed to 294 ADRs. Serious ADRs accounted for 12% of the total ADRs, including acute renal failure (22%), hypo/hyperglycaemia (13%), hyper/hypokalaemia (13%), bone marrow suppression (5%) and hepatic injuries (4%). Three patients died out of the 244 included participants. Polypharmacy, serious ADRs, multiple ADRs, longer time to recover, and longer period of hospitalisation were found to be more frequent among the renal dysfunction group ($p < 0.05$) (Joshua et al, 2007). In another Indian renal unit study of 308 patients, 19% had a 'medication related event' (Castelino et al, 2011).

A prospective cohort study of patients on a Malaysian nephrology ward showed a high rate of 44% ADEs, 22.7% suspected as the cause for admission, and 21.3% happened during admission. The medication classes most frequently involved in ADEs were diuretics, antibacterials, drugs used for diabetes mellitus, antithrombotic agents, mineral supplements and antihypertensive drugs (Hassan et al, 2010). In Dubai, 12.1% of 512 CKD patients experienced an ADR whilst in hospital (Sharif-Askari et al, 2014), and in Israel Zaidenstein et al (2002) found that serious ADEs were developed by 4% of hospitalised patients taking cardiovascular drugs. Those at highest risk were older, were receiving multiple drug therapy, and had higher urea levels indicating RKF.

Anticoagulants and antiplatelets

Anticoagulants have been studied in relation to kidney function and risk of bleeding if blood levels are too high. As discussed in the previous Key review area 2 (2.6.5.6), the Melloni et al (2008) study showed that RKF increased the risk of major bleeding when the anticoagulant GP IIb/IIIa inhibitors such as eptifibitide were prescribed. Cestac et al (2003) and Farooq et al (2004) studied patients with RKF given low molecular weight heparin and found an ADR rate of 10.5% and 8% respectively. The Cestac study was a larger prospective survey (n=334, whilst the Farooq case-note review had 10 participants) and showed that a decrease in creatinine clearance (by 10 ml/min) was associated with an increased haemorrhagic risk (RR = 1.34, 95% CI: 1.12-1.65; $p < 0.05$). Major bleeding occurred in a third of CKD patients who received enoxaparin or heparin during hospitalisation (HR, 4.61 CI: 2.05-10.35) in a Dubai hospital (Sharif-Askari et al (2), 2014). The two case studies discussed in 2.6.5.6 highlighted that the USA anticoagulant dofetilde can cause a significant increase in the QTc interval indicating an adverse effect on the heart (Denetclaw and Dowling, 2011).

Fischer (2013) retrospectively studied 7,413 acute coronary syndrome patients discharged on clopidogrel. There was a significantly higher risk of death for the 34.5% with an eGFR 30-60ml/min/1.73^2 (HR 1.45; 95% CI: 1.18-1.76) and the 11.6% <30

ml/min/1.73^2 (HR 2.48; 95% CI: 1.97-3.13), with an over two fold increased risk of major bleeding.

2.7.6 Summary

Examples of frequent serious ADRs have been shown in well-designed studies from many different countries, although only two studies were found in UK primary care, one on NSAIDs causing hospital admission, and the other on the ineffectiveness of nitrofurantoin prescribed for older people with RKF. The reported figures may be an underestimate as the studies are based on recognised ADRs. Many may have been missed such as a falls that could have been related to high blood levels of some drugs. The inclusion of hospital based studies has shown that the prevalence of RKF related ADRs is high across the sectors, and that further research to identify how to implement effective interventions in hospitals as well as primary care is necessary.

2.8   Key review area 4 – evidence on why prescribers do not apply the recommendations

2.8.1   Research question for key review area 4

Why do prescribers not apply prescribing recommendations in reduced kidney function in primary care?

2.8.2   Identification of relevant studies - search criteria

The search categories were Prescribers 'AND' Guidelines/recommendations 'AND' Prescribing 'AND' Prescriber Behaviour 'AND' Renal impairment 'AND' Primary Care 'AND' English language (see Appendix 3, 0, for the subject headings and key words for each search category). As this search was looking for evidence of why prescribing recommendations are not applied in RKF, the search was limited to qualitative studies. The search term 'review' was added to the Medline search to find any relevant review papers.

2.8.3   Study selection – inclusion/exclusion criteria

Study selection from the search results were based on the following criteria.

Inclusion

- English language.
- Primary empirical qualitative research and reviews of primary empirical qualitative research.
- Relating to prescribing in reduced kidney function.
- Primary care.

Exclusion

- Opinion or discussion articles.

2.8.4   Hierarchy of evidence and appraisal

The research question asks why prescribers not apply prescribing recommendations in RKF in primary care and so a qualitative enquiry would be needed to give an in-depth understanding of human behaviour and the reasons that govern that behaviour.

The OCEBM (Oxford Centre for Evidence-Based Medicine, 2011) states that a systematic review is generally better than an individual study; a meta-synthesis of qualitative studies would aim to combine themes and interpret the thematic findings to generate a new all-encompassing theory. Table 14 shows the hierarchy of evidence

developed for this review where the Level 1 evidence, which would give greatest confidence in the findings, would be a meta-synthesis of qualitative studies relevant to the research question. The table was updated to include 'Related Levels' when no studies were found specifically exploring why recommendations are not applied for prescribing in reduced kidney function. The search was therefore widened to find studies with a more general focus of inappropriate prescribing.

The issues considered when appraising the report of a qualitative study were whether the results of the study were valid, what were the results, and would the results help locally, i.e. in UK primary care. To aid the quality assessment the CASP 'Study checklist' for qualitative research informed the review. The Consolidated Criteria for Reporting Qualitative Research (COREQ) checklist was also used to assess for completeness of reporting and potential for bias in studies of interviews or focus groups (Tong et al. 2007).

2.8.5 Collation and appraisal
2.8.5.1 Description of studies

No studies were found specifically exploring why recommendations are not applied for prescribing in reduced kidney function. The search was then widened to include qualitative studies and reviews on why inappropriate prescribing in general occurs in primary care. Seven studies were included for review (Figure 11). Prescribing errors and potentially inappropriate prescribing were the focus for the 2 meta-syntheses and 1 further study published since. Prescribing decisions was the focus for 3 studies, and 1 on implementation of prescribing guidelines (see Table 15).

hierarchy of evidence	description
Level 1	Meta-syntheses of qualitative studies relevant to the research question.
Level 2	Qualitative studies relevant to the research question.
Level 2b	Qualitative studies relevant to the research question but reduced confidence in applicability e.g. not current.
Level 3	Other studies on prescriber behaviour relevant to the research question.
Related level 1	Meta-syntheses of qualitative studies not specific, but related, to the research question.
Related level 2	Qualitative studies not specific, but related to the research question.
Related level 2b	Qualitative studies not specific, but related to the research question - reduced confidence in applicability e.g. not current.
Related level 3	Other studies on prescriber behaviour not specific, but related to the research question.

Table 14: Hierarchy of evidence table for key review area 4 'why are prescribing recommendations in RKF not applied' developed from the OCEBM Levels of Evidence.

Screened by title	Medline 1,414	Embase 4,019	PsychInfo 293	CINAHL 84	Web of Science 30	Cochrane DARE 0

Screened by abstract, and de-duplicated

7
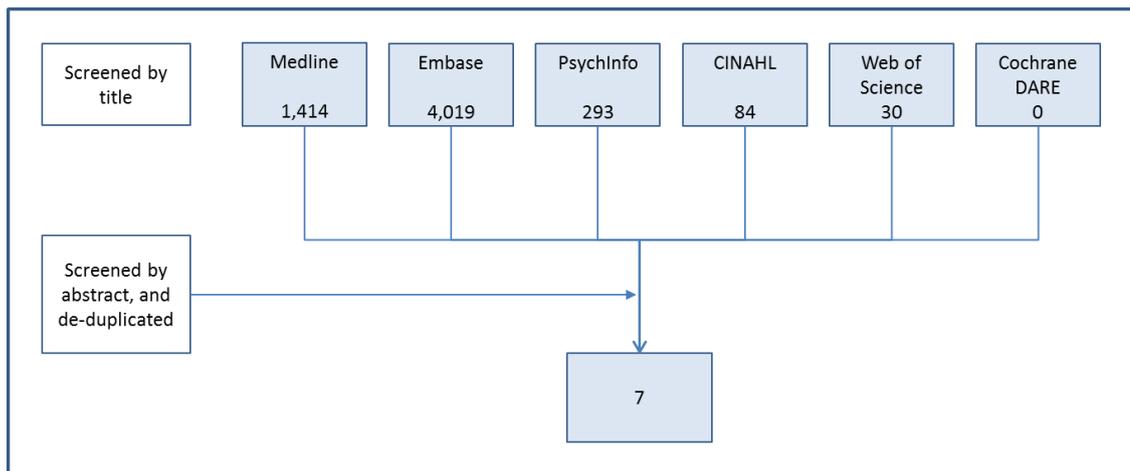
Figure 11: Number of studies identified for key review area 4.

Six of the included studies were published recently. Only the Bradley et al study was not current from 1992, which might mean it is not as relevant to GP behaviour today. Five studies were based in the UK, with the other 2 from The Republic of Ireland and Australia so similar populations and healthcare systems. The 2 meta-syntheses included studies from all healthcare settings, whilst the other 5 studies were all UK primary care based.

2.8.5.2 Heterogeneity

The two meta-synthesis studies included 7 studies (Cullinan et al 2014) and 21 studies (Anderson et al, 2014), with 4 studies common to both as they aimed to explore potentially inappropriate prescribing, with Cullinan focussing on prescribing for older people only. The Slight et al (2013) study was similar to the included studies but was published later. The other 4 studies differed in that they focussed on decision making and implementation of guidelines.

principal author	hierarchy of evidence	year	country	study type	setting	focus	participant type	participant number	outcome
Anderson	Related level 1	2014	Australia	qualitative metasynthesis	all healthcare settings	potentially inappropriate prescribing	medical and non-medical prescribers to adults	21 studies	Many factors were found to be involved which were highly interdependent and impacted by considerable clinical complexity. In polypharmacy, prescribers could not easily identify which medications were inappropriate.
Cullinan	Related level 1	2014	Ireland	qualitative metasynthesis	all healthcare settings	potentially inappropriate prescribing	patients ≥65 years	7 studies	Four key concepts were identified as being causal factors: the need to please the patient, the feeling of being forced to prescribe, tension between prescribing experience and prescribing guidelines, and prescriber fear.
Slight	Related level 2	2013	UK	qualitative interviews	primary care	prescribing errors	interviews: prescribers focus groups: general practice staff	34 interviewed 46 in focus groups	Seven categories of high level error-producing conditions were highlighted: the prescriber, the patient, the team, the working environment, the task, the computer system, and the primary-secondary care interface.
Rashadian	Related level 2	2008	UK	qualitative interviews	primary care	implementation of prescribing guidelines	GPs, 13 academic	25	A change in recommendations may hinder implementation of guidelines, GPs do not have a universal view of valid 'evidence', and use credibility of source or view of influential others to ascertain validity of guidelines.
Solomon	Related level 2	2013	UK	qualitative interviews/ questionnaires	primary care	prescribing decisions	14 patients 8 GPs 2 PCT prescribing advisers	24	85% GPs claimed to use clinical evidence in their prescribing decisions, but most also incorporated patient factors and experience into their decision-making, interpreting guidelines in the context of individual patients.
Bradley	Related level 2b	1992	UK	qualitative interviews	primary care	prescribing decisions	GPs, 5 trainee	74	Highlighted discomfort with prescribing and the struggle to balance several disparate considerations; also that ignorance was a factor but that it was often other things that had more impact such as negotiating change in treatment.
Pressau	Related level 3	2014	UK	questionnaire	primary care	reflective and autonomic decision-making	GPs and nurses	843	Both reflective and impulsive processes predict behaviour and that quality improvement interventions should consider both reflective and impulsive approaches to behaviour change.

Abbreviations: PCT: Primary Care Trust.

Table 15: Studies found for scoping review area 4, listed in order of level of evidence.

2.8.5.3 Methodological quality

As no studies were found specifically exploring why recommendations are not applied for prescribing in RKF, no Level 1-3 studies could be included. The search was expanded to include studies exploring the wider question of why prescribing errors in general occur, prescribing decision-making, and why prescribing guidelines are not always implemented. These studies might highlight some of the determinants likely, but will not be able to show factors specific to prescribing in RKF, for example where monitoring is required and kidney function estimation equations used.

The 2 meta-syntheses studies, rated 'Related level 1', reported that their included papers were good quality, meeting most of the CASP/ COREQ criteria. Common weaknesses were that none of the papers considered the relationship between researcher and participants so researcher bias could not be excluded. Also methods for data collection were not justified or data saturation discussed, and most did not apply triangulation. The other studies included for this review were similar in not giving any indication of the researcher/ participant relationship, and data saturation was not discussed. In 2 studies ethical consideration was not apparent, though both did not include patients (Rashadian et al, 2008; Bradley, 1992). Otherwise the studies met the CASP/ COREQ criteria. Three studies were rated 'Related level 2' as recent good quality qualitative studies. One study was 'Related level 2b' because it was published in 1992 and may need extra consideration as to whether the findings are relevant to prescribers today, and 1 study was rated 'Related level 3' as a correlational questionnaire study of decision-making behaviour.

Neither of the meta-analysis studies discuss whether evidence-based theories were used in their included studies, although the Anderson et al (2014) discuss their results under overall themes of awareness, inertia, self-efficacy and feasibility. The analysis by Slight et al (2013) was informed by Reason's accident causation model (Reason, 1990), Rashidion et al (2008) used the Theory of Planned Behaviour (Ajzen, 1991), and Bradley (1992) used an analysis based on the critical incident technique (Flanagan, 1954). The Presseau et al (2014) study aimed to clarify and combine theoretical models, but the other 2 qualitative studies had no evidenced theoretical base reported.

2.8.5.4 Outcomes - inappropriate prescribing

Anderson et al (2014) report a meta-synthesis of 21 studies to review prescribers' perspectives on factors which shape their behaviour towards continuing or stopping potentially inappropriate medications. They did a COREQ assessment for all included studies finding that 8-22 of the 32 items were reported. A limitation was that many of

the studies focussed on few drug classes (e.g. psychotropic drugs) and only 4 on polypharmacy. The method describes a thematic synthesis. Many factors related to prescribers in stopping, or altering a medication a patient has been on for some time, were found to be involved, which were highly interdependent and impacted by considerable clinical complexity. The themes broadly fell into awareness, inertia, self-efficacy and feasibility. They found that where there was polypharmacy, prescribers could not easily identify which medications were inappropriate.

A meta-synthesis of qualitative studies by Cullinan et al (2014) explored potentially inappropriate prescribing in older patients and aimed to understand why it happens from a prescriber's perspective. Seven papers were included which were assessed as high quality meeting most of the CASP criteria. They describe a clear 7 step method of meta-ethnography used previously in other healthcare research. Four key concepts were identified as being causal factors: the need to please the patient, the feeling of being forced to prescribe, tension between prescribing experience and prescribing guidelines, and prescriber fear. Restrictions to prescribing appropriately were because of a combination of factors, rather than any one dominant factor.

Complex underlying causes of prescribing and monitoring errors in English general practices were highlighted in the recent qualitative study by Slight et al (2013). This was a good quality qualitative study where all CASP criteria were completed, except there was no discussion on the relationship between researcher and participants. They describe semi-structured interviews with GPs on different types of errors. There were also 6 focus groups with a range of practice staff to discuss safeguards in general practice. A thematic analysis informed by Reason's accident causation model (Reason, 1990) was clearly described. Seven categories of high level error-producing conditions were highlighted: the prescriber, the patient, the team, the working environment, the task, the computer system, and the primary-secondary care interface. Some of the error-producing conditions included the prescriber's therapeutic training, drug knowledge and experience, their perception of risk, and the working environment, extensive workload, time pressures, and interruptions. The authors too highlighted the computer-related issues of unnecessary or inappropriate alerts.

2.8.5.1 Outcomes - prescribing decision-making

Solomon et al (2013) report an exploration of prescribing and medicine-taking decisions by patients, GPs and local policy makers. All COREQ criteria were completed, apart from discussion on the relationship between researcher and participants. Semi-structured interviewed with 24 participants were analysed using a 4-step framework analysis. They then used the findings to develop a quantitative

questionnaire which was completed by 305 GPs and 533 patients. The 2 phases were then synthesised. They found that GPs were evidence-based, with 85% claiming to use clinical evidence in their prescribing decisions, but most GPs also incorporated patient factors and experience into their decision-making interpreting guidelines in the context of individual patients.

Presseau et al (2014) investigated prescribing behaviours for hypertension and diabetes in a UK primary care prospective correlational study of GPs and nurses. They concluded that both reflective and impulsive processes predict behaviour and that quality improvement interventions should consider both reflective and impulsive approaches to behaviour change. Prescribing behaviours require the use of an extensive knowledge base, and have strong potential adverse consequences for patient health if performed incorrectly, and so they expected the reflective process to override the impulsive process. However, they found prescribing behaviours were both driven directly by intention, with action planning, and in parallel by automaticity, for blood pressure prescribing. This has implications for designing interventions, as targeting the impulsive system may require a specification of patient and/or environmental characteristics that would cue behaviour automatically.

Bradley (1992) qualitatively sought to understand how prescribing decisions are made in primary care using GP interviews and analysis based on the critical incident technique (Flanagan, 1954). All COREQ criteria were completed, apart from discussion on the relationship between researcher and participants, and also ethical considerations were not discussed. The findings exposed the complexity of decision-making that precedes prescribing. Bradley highlighted discomfort of GPs with prescribing and the struggle to balance several disparate considerations; also that ignorance was a factor but that it was often other things that had more impact such as negotiating change in treatment.

2.8.5.2 Outcomes - clinical guidelines

Rashidian et al (2007) aimed to explore key themes for the implementation of guidelines' prescribing recommendations using a GP interview study in UK primary care. Again all COREQ criteria were reported apart from the relationship between researcher and participants, and also ethical considerations. They reported that a focus on GP's attitudes and personal beliefs may provide a better insight into prescribing than historical work on influencing GPs. The main conclusions were that GPs were critical of guidelines development, relevance and implementation and that future studies should quantify the relationship between the evidence base of recommendations and implementation. Practitioners do not have a universal view of

valid 'evidence', and GPs use credibility of source or view of influential others to ascertain validity of guidelines.

2.8.6 Summary

No research was found specifically on why recommendations are not applied for prescribing for the older patient with reduced kidney function in primary care.

Rigorous and credible meta-syntheses and qualitative studies were found on inappropriate prescribing in general in primary care which highlight that there is complexity in decision making in prescribing and monitoring, and many factors are involved in the underlying causes of errors. Although these studies have explored the factors in UK primary care, there is a need understand the determinants for prescribing in reduced kidney function where regular monitoring is required and application of kidney function estimate calculations, for example, which may be important in developing an intervention that is more likely to be useable and effective.

2.9 Key review area 5 – evidence from UK national guidelines and resources

2.9.1 Research question for key review area 5

What UK national guidelines and resources are available on drug use and dosing in the reduced kidney function of the older person?

2.9.2 Identification of relevant guidance and resources

The most routinely used and recognised resources and national guidelines in primary care were scrutinised:

- The British National Formulary (BNF) was analysed for guidance on prescribing in reduced kidney function as a key resource for prescribers in the UK.
- The regulatory authority drug licence and safety information were considered from the Medicines and Healthcare products Regulatory Agency (MHRA), the Summary of product characteristics (drug licence data sheets, SPCs), and the Food and Drug Administration (United States of America) (FDA).
- The National Institute for Health and Care Excellence (NICE) for England, Wales and Northern Ireland, and the Scottish Intercollegiate Guidelines Network (SIGN), websites were searched for relevant guidelines.
- The Kidney Disease Improving Global Outcomes Foundation (KDIGO) was searched as a global organisation developing and implementing evidence based clinical practice guidelines in kidney disease to improve the care and outcomes of kidney disease patients worldwide.

Any further guidelines found during the literature process would be analysed, and expert advice was sought to ensure the key resources had been included.

Inclusion criteria

Included resources would be in the English language, and be the current guidance for the management of people with reduced kidney function used in the UK.

2.9.3 Collation and appraisal

2.9.3.1 British National Formulary (BNF)

The BNF is a respected resource, and widely used by prescribers for information about drugs in the UK. Prior to 2009, the guidance on use of drugs in 'renal impairment' was presented in the BNF Appendix 3, based on the information provided

in the published SPCs. There was no sign-posting to the guidance in the individual drug monographs.

From 2009, the BNF changed to having the information on use and dosing in reduced kidney function in each drug monograph where appropriate, making it much more accessible. The general guidance on prescribing in renal impairment was moved to a section in the front of the book version. Also in 2009, the BNF started quoting the levels of kidney function in the guidance as 'eGFR' but the figures are still those from the SPCs that are creatinine clearance calculated using Cockcroft Gault. They state that *'although the two measures of renal function are not interchangeable, in practice, for most drugs and most patients of average build and height eGFR (MDRD) can be used to determine dose adjustment in place of creatinine clearance'*, but that *'for potentially toxic drugs with a small safety margin and in some patients (e.g. at extremes of weight) creatinine clearance Cockcroft Gault should be used'*.

After the European guidance on use of the new oral anticoagulants (NOACs) recommended that creatinine clearance should be used to estimate kidney function (Heidbuchel et al, 2013), the BNF drug monographs for dabigatran, rivaroxaban and apixaban were changed from 2014 to specify use of the Cockcroft Gault equation.

2.9.3.2   Regulatory Authorities

For a drug licensed in the UK, the dosing and elimination pharmacokinetic details are set out in the SPCs including dosing in renal impairment, although it is not always relevant or complete (Saldago et al, 3013). Since 2010 the USA Food and Drug Administration (FDA) have required pharmacokinetic studies for new drugs to include both eGFR and CrCl-CG whilst the European Medicines Agency (EMA) still only need 'accurate well established methods' to be used.

The Medicines and Healthcare products Regulatory Agency (MHRA) has issued Drug Safety Alerts relating to use of drugs in RKF, for example for dabigatran and the risk of serious haemorrhage (MHRA, 2012), and ineffectiveness of nitrofurantoin with increased risk of pulmonary adverse events and hospitalisation (MHRA, 2014).

2.9.3.3   Chronic and acute kidney disease guidelines

In 2003 the UK adopted the US Kidney Disease Quality Outcomes Initiative leading to the new chronic kidney disease (CKD) guidelines describing the degree of renal function and detailing clinical care in five stages (Joint Specialty Committee for Renal disease of the Royal College of Physicians of London and the Renal Association, 2005). The National Service Framework (NSF) for Renal Services was introduced in 2005 and in 2006 Quality Outcome Framework (QOF) markers have led to the

formation of registers of patients with CKD stages 3, 4 and 5 as calculated by the MDRD equation to give a glomerular filtration rate estimate normalised for a body surface area of 1.73m^2 (eGFR). Then in 2008 the joint National Institute for Clinical Excellence/Royal College of Physicians (NICE CG73) guideline on CKD and the Scottish Intercollegiate Guidelines Network (SIGN) guideline were introduced to give recommendations for early identification and management of CKD in adults in primary and secondary care.

The NICE/RCP guidelines and the NSF had very little on drugs except the chronic use of non-steroidal anti-inflammatories (NSAIDs) being a risk factor for reducing kidney function and also the use of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin-II receptor blockers (ARBs) in treatment. The NICE guidance was updated in 2014 (NICE CG182) but there is still no guidance on prescribing in RKF apart from 'review the medicines'.

The SIGN CKD guideline (2008) states that kidney function is lower in older people but that '*there is uncertainty as to whether age associated decline in glomerular filtration rate is pathological and should be afforded the same significance as declining function in other situations*'. They do state that '*alterations in drug dosing in patients with reduced renal function should be made on the basis of creatinine clearance as estimated by Cockcroft Gault.*'

> '*Virtually all published recommendations for dose adjustment in patients with reduced renal function, including the British National Formulary (BNF), and manufacturers' summaries of product characteristics are based on creatinine clearance estimated by the Cockcroft-Gault formula. There is no evidence that this estimate can be used interchangeably with the four variable MDRD formula. The current practice of using the Cockcroft-Gault formula for drug dosing should be continued until such evidence is forthcoming*' (SIGN103, 2008, p.11).

Acute kidney injury guidance has been recently introduced (NICE CG169, 2013). This, and initiatives such as the 'Think Kidneys' NHS campaign (NHS England, 2015), include reducing the risk of nephrotoxic drugs on the kidney, and also highlight the need to review use of drugs excreted by the kidney.

The international foundation Kidney Disease: Improving Global Outcomes Foundation (KDIGO) published a paper in 2011 (Matzke et al) on drug dosing consideration in kidney disease. They had many recommendations for clinical practice, further research and regulatory authorities. They recommend that eGFR should be reported in

ml/min rather than ml/min/1.73m^2, as it is never adjusted for body surface area (BSA) in practice. The report did not review prescribing for the older person with RKF as a separate group.

2.9.4 Summary

National and international policies and guidance have advised on management of kidney disease but do not cover dosing of drugs that need altering in the reduced kidney function of the older patient. The introduction of a different kidney function estimation equation for eGFR (MDRD) has not been clarified in relation to use for prescribing decisions for older people.

2.10 Key review area 6 – evidence of intervention evaluation to aid prescribing in reduced kidney function

2.10.1 Research question for key review area 6

Have interventions been evaluated to help prescribers in primary care to apply recommendations for use of drugs in reduced kidney function?

2.10.2 Identification of relevant studies - search criteria

The search categories were 'Decision support tools' AND 'Prescribing' AND 'Renal impairment' AND 'Primary Care' AND 'English language' (see Appendix 3, 0, for the subject headings and key words for each search category). The search term 'review' was added to the Medline search to find any relevant review papers.

2.10.3 Study selection – inclusion/exclusion criteria

Study selection from the search results were based on the following criteria. Although the research question is focussed on primary care, other healthcare settings were included in case the primary care evidence was limited, and for comparison.

Inclusion

- English language.
- Primary empirical research and reviews of primary empirical research.
- Intervention or outcome relating to evaluation of how to improve prescribing in reduced kidney function.

Exclusion

- Opinion or discussion articles

2.10.4 Hierarchy of evidence and appraisal

The research question asked 'does this intervention help', so the OCEBM Levels of Evidence (2011) gives the 'Level 1' evidence, which would give greatest confidence in the findings, to be 'Systematic review of randomised trials, or n-of-1 trial', and individual randomised controlled trials as level 2. Table 16 lists the hierarchy of evidence developed for key review area 6 based on the OCEBM Levels of Evidence. A grade 'b' has been added where the level may be reduced from the ideal, for example where a systematic review is not only of randomised trials. As this search was looking for evidence of intervention evaluation, an RCT method would be the gold standard to research effectiveness (Robson, 2011, p.99). RCTs and reviews of RCTs would be the

studies searched for initially but, as this was a scoping review, the search criteria were left open to capture all relevant studies to give an overview of interventions tried.

The issues considered when appraising were whether the results of the study were valid, what were the results, and would the results help locally in UK primary care? To aid the quality assessment the CASP 'Study checklists' informed the review. Studies were assessed and only included where the focus, methods, recruitment and sampling, valid and reliable objective measurements used, and outcomes were clearly defined, relevant and appropriate to the research question.

hierarchy of evidence	description
Level 1	Systematic review of randomised trials, or n-of-1 trial
Level 1b	Systematic review of prospective trial, not all randomised
Level 2	Randomised trial, or observational study with dramatic effect
Level 2b	Randomised trial, or observational study with dramatic effect; not primary care
Level 3	Non-randomised controlled cohort/ follow-up study
Level 3b	Non-randomised controlled cohort/ follow-up study; not primary care
Level 4	Case series, case-control studies, or historically controlled studies
Level 4b	Case series, case-control studies, or historically controlled studies; not primary care
Level 4c	Non-randomised, non-controlled survey where appropriate
Level 4d	Non-randomised, non-controlled survey where appropriate; not primary care
Level 5	Mechanical-based reasoning

Table 16: Hierarchy of evidence table for key review area 6 'does this intervention help'' developed from the OCEBM Levels of Evidence.

2.10.5 Collation and appraisal

2.10.5.1 Description of studies

Thirty-one relevant studies were found from the database searches (Figure 12) on evaluation of interventions to improve prescribing in reduced kidney function. Table 17 lists the included studies in order of the level of evidence they provide, and whether the intervention had a positive effect or made no change.

All the studies included date from the early 2000s, since CKD national guidelines in many countries were introduced. Computer systems have become more developed in that time, and pharmacist roles have advanced.
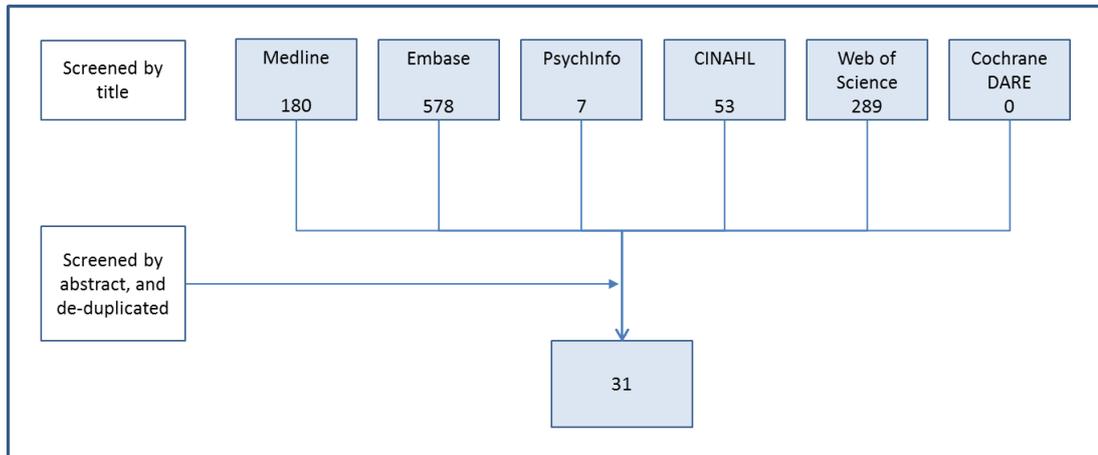
Figure 12: Number of studies identified for key review area 6.

Only one UK based study was found that had some relevance. Avery et al (2012) showed that a pharmacist-led information technology intervention (PINCER) is an effective method for reducing a range of medication errors in general practices with computerised clinical records. They did not include an outcome that assessed the effect on inappropriate prescribing in RKF, but they did find that kidney function testing when taking an ACEI or diuretic could be improved. All but three of the other studies were from countries where the populations are likely to be similar to that of the UK (Western Europe x16, USA and Canada x10, Australia x1) (see Table 17), but healthcare systems and information technology may be different to the UK. Taiwan, Iran, and Saudi Arabia, where the other 3 studies were from, are likely to have populations that differ more from the UK population.

Eleven studies were based in primary care, and 19 were hospital interventions which may be less relevant to a primary care setting, but may give insights into what might be effective or ineffective, especially if there is an assessment of the reasons why.

2.10.5.2 Heterogeneity

The included studies aimed to assess the effectiveness of an intervention, but varied widely in design, focus, population, measures, and outcomes assessed. Some study designs were intervention compared with a control, some were pre and post assessments, whilst others sought to investigate how an intervention was used. The populations studied varied in age, 4 looked at older people; some defined certain drugs to study, such as antibiotics, or a diagnosis such as hypertension or diabetes.

As in the other review areas, kidney function measures were well defined but the estimate equation used, and threshold levels, differed.

The type of interventions were also diverse. Information technology solutions included alerts provided in various forms, and to varying degrees of specificity, and other

decision support tools, either linked to the patient record system, or needing separate operation. Interventions involving pharmacists were investigated in 6 of the studies.

The wide variation means it is inappropriate to make direct comparisons for the whole set of included studies, or pool data. The studies were therefore grouped by healthcare setting to allow comparison, and then further organised into interventions used.

2.10.5.3 Methodological quality

No 'Level 1', but one 'Level 1b' systematic review of studies evaluating CDSS was found (Tawadrous et al, 2011) which addressed a clearly focused relevant question and looked for prospective studies with clinical or patient outcomes, although not all studies were RCTs that would be likely to give the least biased results. Patient-important outcomes such as adverse drug events were considered in 7 of the 32 included studies, which would be the best evidence to show whether there is a reduced risk for patients. All the studies found since this review assessed the intervention effect on reducing inappropriate prescribing, rather than on patient-based outcomes. Although the review was reported within the last 5 years, there have been many studies published since, and computer technology solutions have been further developed, so reviewing more recent literature is likely to add to the evidence.

Four 'Level 2' RCTs based in primary care were found that are the study design most likely to give the least biased evidence for whether an intervention to improve implementation of the recommendations for prescribing in RKF, although there are limitations to each that might reduce the generalisation to UK primary care. The 'PINCER' trial (Avery et al, 2012) was large multicentre, cluster randomised, controlled trial (RCCT) in UK primary care. It was a high quality study which found that the pharmacist led intervention is an effective method for reducing a range of medication errors in general practices, but, more specifically, they assessed whether the intervention could improve the testing of kidney function level for patients taking an ACEI or a diuretic, not whether that reduced inappropriate prescribing.

In the Bhardwaja et al (2011) large RCT conducted in primary care in the USA, of the 244,031 people allocated to the intervention group, 75,560 (31%) had no creatinine clearance measurement. Although this was similar in the control group, it was not possible from their design to assess how many people taking the study drugs did not have a kidney function level available, and whether that was significant for reducing risk of prescribing these drugs. Also, the 20 pharmacies involved would have had participants from both intervention and control groups, so contamination could be possible.

principal author	hierarchy of evidence (based on OCEBM)	year	country	study type	setting	participant number	alerts etc used	outcomes	effect
Tawadrous	Level 1b	2011	Canada	systematic literature review		32 studies		Results promising.	
Erler	Level 2	2012	Germany	randomised controlled trial	primary care	404	CrCl <50ml/min or ≥70 year with hypertension	19.2% vs Patients receiving higher than maximum dose was reduced from 34.5% to 19.2%; but mostly only for ACEI/ARBs	+ve
Field	Level 2	2009	Canada	randomised controlled trial	primary care	833	resident in long-stay unit	Final drug orders were appropriate significanlty more often.	+ve
Avery	Level 2	2012	UK	cluster randomised controlled trial	primary care	10,425	pharmcist led inflromation technology	Significantly less likely to be taking an ACE inhibitor or diuretic without having had urea and electrolytes measured in the preceding 15 months.	+ve
Bhardwaja	Level 2b	2011	USA	randomised controlled trial	hospital	6,125	CrCl <50ml/min taking 1 of 15 study drugs	Error reduced from 49% to 33% (p<0.001).	+ve
Farag	Level 3	2014	Canada	retrospective time-series analysis	primary care	1,464	66 years or older with CKD stages 4 or 5	Introduction of eGFR reporting had no impact on the rate of inappropriate antibiotic prescribing in RKF.	no change
Czoch	Level 3b	2015	Germany	prospective cohort	hospital	1,012	make more patient and drug specific	Tailoring reduced alert burden.	N/A
Diaz	Level 3b	2013	Spain	non-randomised, pre-post-test	hospital	28 patients /day	for pharmacists when RKF	65% appropriate increased to 86% (p<0.001).	+ve
Kalender-Rich	Level 3b	2011	USA	retrospective time-series analysis	hospital	260	>70 years with RKF	Automated eGFR reporting was associated only transiently with improved dosing appropriateness.	no change
Melton	Level 3b	2015	USA	quantitative pre and post, and qualitative	hospital	20	to assess alert usability	43% fewer prescribing errors with the redesigned alerts (p=0.001).	+ve
Quartorolo	Level 3b	2007	USA	retrospective and prospective time-series analysis	hospital	260 before 198 after	reporting of eGFR	No significant change in inappropriate prescribing of NSAIDs or antibiotics.	no change
Wang	Level 3b	2012	Taiwan	prospective time-series analysis	hospital	38,647	antibiotic prescriptions	Inappropriate prescribing was decreased by 80%.	+ve
Via-Sosa	Level 4	2013	Spain	historically controlled cohort	primary care	354	CrCl <60 ml/min	Community pharmacies can increase the proportion of adequate drug dosing.	+ve
Desmedt	Level 4b	2012	Belgium	prospective case control	hospital	615	for prescribers when eGFR<60ml/min	Slight decrease in inappropriate prescribing (non-significant) - physicians often ignored the alerts.	no change
Falconnier	Level 4b	2001	Switzerland	prospective case control	hospital	1,648	CrCl ≤50 ml/min	81% adjusted to renal function, compared with 33% in the control group.	+ve
Forough	Level 4b	2014	Iran	case control	hospital	137	text alert to physician if CrCl <50ml/min	significant increase in dose alteration (p<0.001), but not for drug discontinuation	+ve

Sellier	Level 4b	2009	France	case control	hospital	603	for prescribers, re 24 drugs when eGFR reduced	Inappropriate prescribing did not reduce with alerts.	no change
Barnes	Level 4c	2014	USA	prospective survey	primary care, care home	146	pharmcist dosing service	Dosing recommendations made for an average of 1 per patient and the GP accepted 65.2%.	+ve
Geerts	Level 4c	2012	Netherlands	prospective survey	primary care	650	Aged > 70 years with diabetes or CVD	13.7% therapeutic recommendations for patients aged >70 years with diabetes or cardiovascular disease.	+ve
Gheewala	Level 4c	2014	Australia	survey	primary care	28	care home resident with CKD	83.8% of recommendations made by the pharmacist were accepted by GPs.	+ve
Joosten	Level 4c	2013	Netherlands	prospective survey		1,369	for community pharmacists when eGFR<40ml/min	A medication error was detected in 15% of the alerts, most were significant or serious.	+ve
Boussadi	Level 4d	2013	France	prospective survey	hospital	3,228	for pharmacists when RKF	Alerts highlighted more errors than pharmacist review.	+ve
Cho	Level 4d	2014	USA	retrospective survey	hospital	584	for prescribers when RKF	78.2% alerts were over-ridden.	no change
Frolich	Level 4d	2011	Switzerland	cross-sectional survey	hospital	509	RKF	CDSS identified a large number of alerts	N/A
Garcia-Molina	Level 4d	2013	Spain	prospective survey	hospital	29	CrCl < 60ml/min	Pharmacist found 21% of renal risk drugs needed dose adjustment	+ve
Hudali	Level 4d	2015	USA	survey	hospital	6	antibiotics in RKF	Errors reduced from 15.4% to 3.7% (p<0.001).	+ve
Nielson	Level 4d	2014	Denmark	prospective survey	hospital	232	eGFR 10-49 ml/min/1.73m^2	Inappropriate dosing continued after automatic eGFR reporting.	no change
Youseff	Level 4d	2015	Saudi Arabia	retrospective survey	hospital	314	for prescribers when RKF	Alerts over-riden - 14% contra-indicated but administered despite alert.	no change
Geerts	Level 5 (feasibility)	2013	Netherlands	feasibility study	primary care	50	40 patients,5 GPs, 5 pharmacy staff	Point-of-care creatinine testing feasible in a community pharmacy.	N/A
Helldén	Level 5 (pilot)	2015	Sweden	pilot: qualitative questionnaire and focus group	primary care	8	GPs	Approved automatic presentation of CrCl status on opening the medication list, and ability to actively look up specific drug recommendations in two steps.	N/A
Shemeikka	Level 5 (pilot)	2015	Switzerland	proof-of-concept; questionnaire	hospital	86	physicians	Pilot of CDSS well received.	N/A

Abbreviations: CDSS: computer decision support system; CKD: chronic kidney disease; CrCl: creatinine clearance; CVD: cardiovascular disease; eGFR: estimated glomerular filtration rate; RKF: reduced kidney function.

Table 17: Studies found for scoping review area 6, listed in order of level of evidence.

Similarly, in the Field et al (2009) RCCT, physicians would prescribe in both intervention and control groups, even though the healthcare units were randomly allocated,.

The follow-up analysis of the Erler et al (2012) RCCT revealed that the effect was mostly related to ACEIs and ARBs, even though the dosing software covered 800 drugs, which might reduce the usefulness for all drugs affected by kidney function. Sample size calculation was used, but only 10 patients per practice were recruited which might have reduced the capacity of the study to pick up a wider drug effect range.

Studies that are not randomised and controlled are more likely to be subject to biases that might weaken confidence in the results. Where the intervention and control groups are not randomly allocated, confounding factors may not be the same for each group, and in pre and post studies there may be changes over time.

As discussed in Chapter 1 (1.4.2) an intervention is more likely to be effective if it is developed on evidence-based principles of behaviour change (Cane et al, 2012). Only the PINCER study protocol (Avery et al, 2009) discussed using theory to develop their intervention; they used the principles of Human Error theory (Reason et al, 2000) to consider the causes of medication errors in primary care from their literature review and empirical research. No other included study defines evidence-based theory for the development of their intervention other than having found a problem.

2.10.5.4 Intervention outcomes: UK primary care

No studies were found that specifically aimed to provide evidence of what intervention evaluation to help prescribers in UK primary care to apply recommendations for use of drugs in reduced kidney function.

The 'PINCER' large multicentre RCCT found that a pharmacist-led information technology intervention was an effective method for reducing a range of medication errors in UK general practices with computerised clinical records (Avery et al, 2012). They included one kidney related outcome, finding that patients aged 75 years and older in the intervention group were significantly less likely to be taking an ACE inhibitor or diuretic without having had kidney function measured in the preceding 15 months. Having a recent kidney function test available is required to be able to prescribe according to the recommendations, but this study does not provide evidence for whether this would translate to appropriate prescribing.

2.10.5.5 Intervention outcome: reviews

Tawadrous et al (2011) systematically reviewed 32 studies using clinical decision support systems (CDSS) for kidney-related drug prescribing. This was a well reported review which focussed on prospective studies reporting clinical and/or patient outcomes, but a limitation was the heterogeneity of the designs. The studies were mostly in academic hospital settings and in 17 studies decision support systems were computerised, whilst in 15 studies they were manual pharmacist-based systems. Systems prompted for drug dosing adjustments in relation to the level of decreased kidney function (25 studies) or in response to serum drug concentrations or a clinical parameter (7 studies). For computerised systems, clinician prescribing outcomes, such as frequency of appropriate dosing, were considered in 11 studies, with all 11 reporting statistically significant improvements. Similarly, manual DSSs that incorporated clinician prescribing outcomes showed statistically significant improvements in 6 of 8 studies. Patient-important outcomes such as adverse drug events were considered in 7 studies of CDSSs, with statistically significant improvements in 2 studies. For manual DSSs, 6 studies measured patient-important outcomes and 5 reported statistically significant improvements. The authors concluded that the results were promising; however, only 2 of 5 studies looking at patient-important outcomes from computerised CDSSs were beneficial which shows that further research is required.

2.10.5.6 Intervention outcomes: primary care based from other countries

Reporting of eGFR - primary care

The universal reporting of eGFR might have been expected to improve awareness of kidney function and so allow prescribers to apply the results to prescribing. Dosing errors for antibiotics in older people with CKD stages 4 or 5 were assessed before and after the introduction of eGFR reporting in a primary care time-series analysis in Canada (Farag et al, 2014). Reporting of eGFR had no impact on the error rate (68 per 100 antibiotic prescriptions; $P = 0.9$). Nitrofurantoin, which is contraindicated in patients with CKD, was prescribed 169 times throughout the study period. The authors state that they 'attribute the dosing errors to poor awareness of dosing guidelines' but they 'did not assess physician knowledge to confirm this'.

CDSS - primary care

Erler et al (2012) used a multi-faceted intervention in an RCCT in primary care practices in Germany. Using a cluster design meant there was a reduced likelihood of contamination between the groups, but blinding was not possible. The intervention of a workshop, desk-top checklist, patient information and dosing software for over 800

drugs was aimed at prescribers. Forty-six practices were randomly allocated to intervention or control, the practices identified a list of potential participants and then 10 patients per practice were randomly identified for the study. In 404 participants (198 intervention and 206 control) the proportion of patients receiving one or more prescriptions exceeding the recommended maximum daily dose was significantly lower in the intervention group after 6 months: 19.2% vs 34.5% for the control group (OR = 0.45, 95% CI: 0.29-0.70; p<0.001). However, follow-up analysis revealed that the effect was mostly related to ACEIs and ARBs which might reduce the usefulness for all drugs affected by kidney function. The dosing software provided was well received, but it could not integrate with the patient record system and so the prescriber needed to remember to use the system for affected drugs, which might be why few drugs were altered. Sample size calculation was used, but only 10 patients per practice were recruited which might have reduced the capacity of the study to pick up a wider drug effect range.

The Canadian RCT in 22 long-term care facilities aimed to assess whether CDSS with an alert would improve prescribing in RKF over 12 months (Field et al, 2009). The randomisation was done by unit, though the method was not clear, and the intervention and control groups were shown to be very similar. Alerts were triggered when a physician ordered a listed drug for a patient with a reduced creatinine clearance, and rates of alerts were similar for each group. It isn't clear from the report whether there was blinding at any stage, and the authors do highlight that physicians would prescribe in both intervention and control groups. The control group continued to have the current creatinine clearance displayed as had been happening prior to the study. Significantly higher proportions of final drug orders were appropriate in the intervention units: relative risk 2.6 for drugs that should be avoided (95% CI: 1.4, 5.0), 1.8 for alerts to acquire missing information (95% CI: 1.1, 3.4), and overall final drug orders were appropriate significantly more often in the intervention units relative risk 1.2 (95% CI: 1.0, 1.4). However, the system did not improve the rate at which appropriate doses were ordered, partly because the control group showed high levels of appropriate dosing.

Helldén et al (2015) in Sweden has reported a proof-of-concept study of a CDSS in primary care. This qualitative questionnaire and focus group study found the automatic presentation of the creatinine clearance status on opening the medication list, and the ability to actively look up specific drug recommendations in two steps was appreciated. The GPs wanted to continue the use of the CDSS and to recommend it to others.

Pharmacist based intervention - primary care

A large randomised controlled trial (n=32,917) showed alerts to pharmacists significantly reduced errors from 49% to 33% (p<0.001) in ambulatory care in the USA (Bhardwaja et al, 2011). This study clearly set out the focus and methods, with blinded random allocation, similar intervention and control (usual care) groups, and a blinded research pharmacist to decide whether there had been a true medication error. An alert was triggered in the dispensing pharmacy for patients with CrCl-CG <50ml/min prescribed one of the 15 investigation drugs; however, of the 244,031 people allocated to the intervention group, 75,560 (31%) had no creatinine clearance measurement. Although this was similar in the control group, it was not possible from their design to assess how many people taking the study drugs did not have a kidney function level available, and whether that was significant for reducing risk of prescribing these drugs. The 'usual care' group had a high level of medication errors reported, 49%, even though the 20 pharmacies involved would have had participants from both intervention and control groups. The alert intervention, which would not allow the prescription label to be printed, did result in a significant reduction of errors, but at 33%, a third of people were still at risk from their medication.

Joosten et al (2013) reports in their survey that a medication error was found in 15% of alerts generated where eGFR <40ml/min/1.73m^2 for community pharmacists in The Netherlands, and most were significant or serious. There were 1,369 alerts which was 5.3% of all creatinine assays done, and the median age of patients was 78 years. The pharmacists recommended 342 medication changes, with 66% accepted by the physician. This was not a controlled study, but does show the concept that allowing community pharmacists to have renal data can significantly reduce serious errors. The authors suggest that this can be done relatively straight forwardly with minimal expense.

Three further studies showed that community pharmacy interventions might be useful to reduce the risk of harm. Geerts et al (2013) showed that it was feasible for Dutch community pharmacists to test kidney function and advise GPs where alterations to prescribing were needed. They had previously shown in a prospective survey that community pharmacists provided with kidney function level by the GP practice, and using alerts, resulted in 13.7% therapeutic recommendations for patients aged >70 years with diabetes or cardiovascular disease, although only half were agreed by the GP (Geerts et al, 2012). A non-randomised historically controlled study in Spain showed community pharmacist intervention improved appropriate prescribing for older

people with RKF, although only a third of recommendations were followed through by GPs (Via-Sosa et al, 2013).

A survey of a pharmacist review service to care homes in Australia identified inappropriate prescribing of renally cleared medications in 16% of residents with CKD; in this study 83.8% of recommendations made by the pharmacist were accepted by GPs (Geewala et al, 2014). Also in a pharmacist service to care homes in the USA, dosing recommendations were made for an average of 1 per patient and the GP accepted 65.2% (Barnes et al, 2014).

2.10.5.7 Intervention outcomes: hospital based

Reporting of eGFR - hospital

Reporting of eGFR has been associated with improved physician recognition of chronic kidney disease in elderly hospitalised patients in California, but it did not lead to a change in physician prescribing in a retrospective and prospective time-series analysis (Quartarolo et al, 2007). There was only a transient effect of eGFR reporting on dosing for patients aged ≥70 years in the USA (Kalender-Rich et al, 2011), and in Denmark inappropriate dosing continued after automatic eGFR reporting (Nielson et al, 2014).

Alerts - Hospital

Three hospital studies found alerts to prescribers led to reductions in inappropriate prescribing when kidney function is reduced. Hudali et al (2015) used a survey design to look at the effect of an alert on prescribing antibiotics as recommended in RKF and found a highly significant reduction in errors from 15.4% to 3.7%. A text alert when CrCl-CG was less than 50 ml/min led to a significant increase in dose alteration (p<0.001), but not for drug discontinuation, in a case-control study (Forough et al, (2014). Melton et al (2015) reported a qualitative exercise and a redesign of their alerts; when they then tested the new alert there were 43% fewer prescribing errors compared with the original alerts (p = 0.001). When laboratory links were presented on the redesigned alert, laboratory information was accessed 3.5 times more frequently.

Other studies revealed some problems with alerts. Both Cho et al (2014) and Youssef et al (2015) found that alerts were overridden. In the former retrospective survey on renal alerts, 78.2% were overridden. 14% of the alerts in the latter were contra-indications but were still administered to the patient; multivariate logistic regression showed that the odds of receiving the contraindicated drugs increased in those with severe renal insufficiency (OR = 23.4, 95% CI 9.9-54.9, p < 0.001) after adjusting for confounding factors. The Desmedt et al (2012) prospective case control study also

found alerts were ignored and they did not find a significant reduction in prescribing errors. Sellier et al (2009), in another case-control study, found that inappropriate prescribing did not reduce with alerts.

Frolich et al (2011) surveyed the effect of a CDSS and found it generated a large number of alerts. For the 2,729 prescriptions written for the 509 patients enrolled in the study there were generated 2,558 interaction alerts and 1,849 comments, with only a minor fraction likely to be of substantial risk to the patient. Czock et al (2015) used a prospective cohort study to show that a non-specific alert system would yield an average number of alerts per medication regimen of 2.22, but by tailoring alerts to be patient and drug specific, the alert burden was reduced by 90% to 0.094 per medication regimen.

CDSS – hospital

In a recent study, a CDSS to support prescribing in RKF using an integrated electronic health record system was piloted in a geriatric clinic, an internal medicine admission ward and two outpatient healthcare centres (Shemeikka et al, 2015). In total 86 physicians completed an initial questionnaire about their expectations on the CDSS, there was a focus group discussion after 5 weeks, and a follow-up questionnaire was completed at the end. It was well received with 97% wanting to continue using it.

Wang et al (2012) describe the development of a CDSS for antibiotic prescribing in RKF. The instances of inappropriate antibiotic dosage prescriptions were decreased by approximately 80% after the calculator was implemented (RR, 0.18 - 0.23; $p < 0.001$), and the incidence rates of renal function deterioration were lowered from 12.39% to 9.47%. The frequency of antibiotic calculator utilisation by physicians increased from 239 times per year in 2005 to 3,480 times per year in 2008, and the acceptance rate of the calculator's dosage recommendations went from 68.2% in 2005 to 94.7% in 2008. The average acceptance rates of pharmacist recommendations by physicians were 97.7%.

Pharmacist based intervention - hospital

Falconnier et al (2001) used a case-control study to show that using immediate concurrent feedback by pharmacists, the dose of 81% of renally eliminated drugs in patients with CrCl-CG ≤50ml/min were adjusted to renal function, compared with 33% in the control group. In a non-randomised, pre-post intervention study, Diaz et al (2013) assessed a CDSS that helped pharmacists to identify patients with RKF, identify medication orders that may require dosage modifications based on renal function, and generate an alert with a recommendation of specific dosage adjustment.

Before the intervention, the frequency of appropriate prescribing based on kidney function was 65%, and after was increased to 86% (p<0.001).

Two prospective surveys also suggest that alerts can aid pharmacists in highlighting errors. Boussadi et al (2013) found a clinical decision rule-based alert system for drug dose adjustment in patients with renal failure helped pharmacists to find errors, and suggest that an alert system would be complementary to the pharmacists' activity, contributing to drug prescription safety. A pharmacist intervention for drug dosage adjustment of renal risk in patients with RKF during their admission found 293 renal risk drugs in 29 patients, 21% of them required a dose adjustment (Garcia-Molina et al, 2013).

2.10.6 Summary

This review found no studies evaluating interventions to help prescribers in UK primary care to apply recommendations for use of drugs in reduced kidney function. The reporting of eGFR might have raised awareness of kidney disease but studies in both primary care and hospital have shown that it has not improved prescribing in RKF. Evaluations of alerts and more sophisticated CDSSs have shown mixed results, but the studies that investigated pharmacist-led interventions all showed reductions in inappropriate prescribing. None of the studies found aiming to improve prescribing in RKF were based on theory or determinants of why prescribing was not appropriate, which might be a factor for studies not showing benefit if the intervention was not addressing the barriers.

2.11 Discussion

Six key areas were identified for this scoping literature review using the mind map developed from the findings of the pilot case-note review study (2.4.1.1, Figure 7). The mind map has been developed further in Figure 13 to summarise how knowledge, themes, and implications for ongoing research have been developed through the key findings.

Key review areas	UK primary care evidence	Evidence from other UK settings	Evidence from other similar countries or related fields	Key themes	Implications for further research
1. To what extent are older patients on drugs and doses not recommended at their level of kidney function in primary care?	None found, other than the pilot case-note review.	2 studies only found in UK hospitals: 25% and 56% of prescribing was found to be inappropriate for older people with RKF.	Evidence from many countries show there is a high level of inappropriate prescribing in RKF (17-83%), particularly for older people.	• High prevalence of inappropriate prescribing in RKF. • Many drugs are implicated. • Old age is a risk factor.	An investigation is needed into the prevalence of inappropriate prescribing in RKF in a wider population of older people in UK primary care.
2. How should kidney function be estimated when informing dosing decisions for older people.	In many countries, patient outcome and drug blood level studies have shown that there is a significant difference between the CG and MDRD equations used for older people, and that CG is the better estimate for drug dosing. eGFR overestimation increases with the age of the patient. Many different drugs have been highlighted as potentially being affected by which equation is used e.g. antihypertensives including ACEIs, NSAIDs, NOACs, metformin, antibiotics.			• CG should be used for prescribing decisions. • eGFR overestimates for older people, increasingly with age. • Many drugs are implicated	There is a need to investigate the prevalence using CG, and how many patients would be missed for drug alteration if eGFR is used in UK primary care.
3. What are the risks to the patient of not following recommendations?	Only 2 studies found: NSAIDs caused AKI and hospital admission, and nitrofurantoin was ineffective in RKF.	1 small study showed an 8% ADR rate for heparin used in RKF.	Increased mortality by 40%, admissions, and ADRs (3-62%), some serious, were caused by inappropriate prescribing in RKF.	Inappropriate prescribing in RKF causes: • Increased mortality • ADRs, hospital admissions • E.g. NSAIDs, anticoagulants	The risk of harm and hospital admission emphasises the need for research into how to reduce inappropriate prescribing in RKF.
4. Why do prescribers not implement prescribing recommendations in reduced kidney function in primary care?	None found.		2 meta-syntheses, and UK primary care studies, on inappropriate prescribing show complex interdependent determinants	Prescriber – lack of problem awareness, fear of consequences of change, personal ability. Extrinsic – feasibility of altering, experience vs guidelines	An exploration of prescriber behaviour related to prescribing in RKF in UK primary care is needed to ensure relevant factors are recognised.
5. What guidelines and resources are available on drug use and dosing in the reduced kidney function of older people?	UK: the BNF gives the SPC recommendations in RKF in the drug monograph, but labels the figures as eGFR, except for NOACs, rather than the CrCl that they are in the SPC – it states they are similar for most but gives the CG equation for high risk. NICE CKD guidance only states to 'review the medicines'.		KDIGO has published a paper on drug dosing in kidney disease but there was no assessment for older people as a separate group.	• BNF presentation does not fit the evidence for older people. • NICE does not provide guidance for prescribing in RKF.	Evidence in UK primary care needs to be stronger to support clarification of the BNF guidance, and NICE CKD & AKI guidance .
6. Have interventions been evaluated to help prescribers in primary care to apply recommendations for use of drugs in reduced kidney function?	None found. 1 study found that showed pharmacists can improve kidney function testing when a patient is on an ACEI or diuretic.	None found.	Universal reporting of eGFR has not improved prescribing. Studies involving pharmacists showed positive results. IT solutions e.g. alerts showed mixed results.	• Pharmacist interventions have a positive effect. • Alerts have mixed effects. • No studies informed by evidence-based behaviour theory.	A behaviour change theory based intervention for UK primary care needs to be developed and tested to reduce inappropriate prescribing.

Abbreviations: ACEI: angiotensin-converting enzyme inhibitor; ADR: adverse drug reaction; AKI: acute kidney injury; BNF: British National Formulary; CrCl: creatinine clearance; CG: Cockcroft Gault; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; KDIGO: Kidney Disease Improving Global Outcomes Foundation; MDRD: Modification of Diet in Renal Disease equation; NICE: National Institute for Health and Clinical Excellence; NOAC: Novel oral anticoagulant; NSAID: non-steroidal anti-inflammatory; RKF: reduced kidney function; SPC: summary of product characteristics.

Figure 13: Summary of the literature review findings in the 6 key review areas from the mind map (Figure 7)

2.11.1 Description of included studies

The Cockcroft Gault equation to calculate creatinine clearance was introduced in 1971 to estimate kidney function (Cockroft and Gault, 1971), but most of the studies identified for this review were from the early 2000s onwards. Very few studies on prescribing and RKF were found before 2000; in Lazarou and Pomeranz's USA review (1998) it was reported that kidney function was a factor rarely reported in the studies sampled and so they could not determine the effect on ADR rate. CKD guidelines began to be published in many countries in the early 2000s. In the UK it was 2005 when the first were introduced (Joint Specialty Committee for Renal disease of the Royal College of Physicians of London and the Renal Association, 2005), and most of the studies date from that time onwards suggesting an increased awareness of kidney function in relation to prescribing. The development of computer systems, and of pharmacist roles, over this time also seems to have been a factor in the more recent studies undertaken.

Very few studies were based in UK primary care which would give the best local evidence for this review, particularly for the prevalence questions, and where the healthcare system and working environment might be important. However, studies from countries with similar populations were found that have given key themes and implications for research in the UK.

The first primary care studies were published from the mid-2000s, with the earlier studies being hospital based. The hospital studies have tended to investigate drugs used for more acute conditions and acutely ill patients, with different healthcare processes, and so the results may not be as applicable to UK primary care. The prescribing systems and procedures are different in primary care to those in hospitals, including advanced computerised patient record systems used in UK primary care that might mean different findings to hospital based studies. However, inclusion of hospital based studies has shown that the prevalence of recommendation non-compliance is high across the sectors, and that further research to identify how to implement effective interventions in hospitals as well as primary care is necessary.

The research questions focussed on older people, and studies were found that had older participants only, although the definition of 'old age' differed with thresholds from 65 years to 85 years cited. However, other studies were included as many discussed that older people are more likely to have reduced kidney function, and statistical analyses in some across ages highlighted old age as a 'risk factor'. Older mean ages were reported, even if the study design was not specifically to study older people, for

example, means ages of 70 years (Salomon et al, 2003), 73 years (Pillans et al, 2003), and 75 years in the Flaconnier et al (2001) study.

This review has highlighted that kidney function was measured and calculated in different ways in the included studies, and the thresholds used varied widely in the studies found, making it not possible to make precise comparisons. It has also shown that many patients did not have a kidney function estimate on their record, even though they were prescribed drugs that would require adjustment if kidney function was low. This could also mean that these studies are reporting an underestimate of the problem.

2.11.2 Methodological quality

A limitation of the Arksey and O'Malley scoping review method is that it does not formally appraise the quality of evidence (Arksey and O'Malley, 2005). It remains unclear whether not including quality assessment impacts the uptake and relevance of scoping study findings (Levac et al, 2009). The current study included an assessment of the quality to give an indication of where the current literature is of sufficient quality to answer the research question, and whether there is a need for further investigation to have greater confidence in the findings. By including a quality assessment, to be feasible, only published studies were included, and opinion and discussion articles were excluded, introducing a limitation, the risk of publication bias, and reducing the breadth of the investigation. The quality of the studies found was appraised using standard checklists such as CASP and COREQ, assessing for validity, the extent to which conclusions of each study were supported by the results presented and consistent with the methods used, and for reliability, whether the methods were reported in sufficient detail to repeat the study and obtain similar conclusions.

The hierarchy of evidence tables developed for each key area allowed a systematic assessment of the appropriateness of study design for the research question and methodological quality. By ordering the studies by the level of evidence and quality, it has shown the lack of 'Level 1' UK primary care based studies that would give generalisable evidence in a UK setting. It has highlighted that no UK primary care based studies were found to show:

- To what extent older people are on drugs and doses not recommended at their level of kidney function in primary care.
- What the risks are to the older patient of not following the recommendations in UK primary care.

- Why prescribers do not apply the recommendations for prescribing in RKF in primary care.
- What interventions are needed to help prescribers in UK primary care to apply recommendations for use of drugs in reduced kidney function.

A systematic review is generally better than an individual study (Oxford Centre for Evidence Based Medicine, 2011), but only one systematic review was found overall, and that did not only include RCTs that would be the best evidence for intervention studies (Tawadrous et al, 2011). It is a good quality systematic review of interventions to improve prescribing in RKF, and more recent studies found have added to the findings, although only 4 of 30 of those were RCTs. Narrative reviews were found for the prevalence, kidney function equation, and ADR reviews, although they were found to have some issues that need to be considered. The Long et al (2004) review was over 10 years old and found very few prevalence studies, whilst many studies have been published since that would give a better, more up to date indication, such as the high quality, large, multi-centre, French primary care prospective cohort study (Breton et al, 2011). Four narrative reviews on the use of kidney function estimation equations were found; Helou (2010) did not review use of the equations for prescribing, but did look at the issues for older people, and Spruill et al (2008) looked at mathematical comparisons only. The other two reviews did look at prescribing for older people, but neither gave the method used for study identification, making it not possible to assess whether there was bias in the selection. The one narrative review found looking at the risks of not applying prescribing in RKF recommendations, also gave no method for study selection (Marcum and Fried, 2011). Two good quality meta-syntheses were found that gave insights into inappropriate prescribing, but none were found looking specifically at the determinants for prescribing in RKF.

Much of the evidence found is 'non-local', reducing the level of evidence assigned. In the kidney function equation review, the locality is less important for the assessment of calculation, but would be when considering the effect of methods of assay and of reporting. In this review over half the studies were assigned a 'Level 5' as they were 'mechanical reasoning' only; however, these studies are useful in highlighting the large range of drugs that could be affected, especially when prescribed for older people.

As has been highlighted in previous sections, many of the studies need a kidney function estimate available for the analyses, and participants are excluded where it cannot be extracted. Retrospective studies are more likely to be affected by this as they are reliant on whether the data was collected at the time, whilst prospective studies allow collection specifically for the study if needed. For example, in the large

Corsonello et al retrospective study (2005), 5,499 (32%) of the patients had to be excluded, most of whom because a kidney function estimation was not available, whereas the prospective study by Blix et al (2006) only needed to exclude 2.3%. Some studies, like Corsonello, analysed the participants who were excluded to show that they were similar to the study population, but it is still unknown what the kidney function levels are for that group, and whether it might change the findings of the study, introducing potential bias. Confidence in the findings for the population are reduced, but it does highlight a problem of kidney function not being applied even though drugs affected by RKF are prescribed. This suggests a need to check whether kidney function is checked regularly in UK primary care for people prescribed drugs with recommendations for altered use in RKF.

As discussed in Chapter 1 (1.4.2), changing behaviour is more effective if interventions are developed on evidence-based principles of behaviour change (Cane et al, 2012), and using a theoretical approach allows identification of factors and strategies that are more likely to be successful in influencing behaviour change (Nilsen, 2015). However, none of the studies found aiming to improve prescribing in RKF (review area 6) were based on theory or determinants of why prescribing was not appropriate, which might be a factor for some of the studies not showing benefit if the intervention was not addressing the barriers. Only the PINCER study protocol (Avery et al, 2009) discussed using theory to develop their intervention; they used the principles of Human Error theory (Reason et al, 2000) to consider the causes of medication errors in primary care from their literature review and empirical research. However, this high quality study, although showing that the pharmacist led intervention is an effective method for reducing a range of medication errors in general practices, did not study specifically whether it would reduce inappropriate prescribing in RKF.

Whilst recognising the limitations found for some studies in the methods used and reported, overall, this scoping literature review has found a wide range to outline what is already known, and identity gaps in the existing published literature, on the issues relating to prescribing for older people with reduced kidney function in UK primary care.

2.11.3 Principal findings

Figure 13 summarises how knowledge, themes, and implications for ongoing research have been developed through the key findings in this scoping literature review.

2.11.3.1 Prevalence

No studies were found that would give prevalence data in UK primary care for inappropriate prescribing in RKF. Evidence from other countries, and from the hospital setting, shows that prescribing for patients with reduced kidney function does not always follow the recommendations. The high quality, large, multi-centre, French primary care prospective cohort study (Breton et al, 2011), and the UK hospital case-record analysis (Jones and Bhandhari, 2013), give a good indication that there may be a problem in UK primary care and that it should be investigated. Across the studies, many drugs have been found to be prescribed inappropriately in RKF (Breton et al, 2011; Khanal et al, 2015; Emami et al, 2012), and drugs mentioned frequently include:

- ACEIs,
- Antidiabetic drugs, such as metformin.
- Bisphosphonates, such as alendronic acid.
- Lipid-lowering drugs, such as simvastatin.

Old age has been highlighted as a risk factor, for example, Khanal et al (2015) showed that the factors independently associated with patients being prescribed one or more potentially inappropriate renally cleared drugs included advancing age. Many good quality studies have highlighted the extent of inappropriate prescribing in older people with RKF (Breton et al, 2011; Schmidt-Mende et al, 2012; Khanal et al, 2015).

The findings of this review suggest that an investigation is needed into the prevalence of inappropriate prescribing in RKF in a wider population of older people in UK primary care than the pilot case-note study.

2.11.3.2 Kidney function assessment for prescribing decisions for older people

Patient outcome and drug blood level data shows that the Cockcroft Gault calculation should still be used to estimate kidney function for drug dosing decisions, in particular for the older patient (Melloni et al, 2008; Roberts et al, 2008). Four review papers all conclude that the MDRD equation for eGFR should not be used for drug dosing decisions (Spruill et al, 2008; Hellou, 2010; Nyman et al, 2011, Hudson and Nyman, 2011). Using eGFR to inform prescribing decisions has been shown to overestimate the kidney function level, and that the effect increases with age meaning that the greatest risk is for the oldest patients (Roberts et al, 2008). Using eGFR would mean that patients who should have their drug treatment altered might be missed (Melloni et al, 2008). It is also clear that the prescribing decisions for many drugs would be

affected by which equation is used; examples include gabapentin, antibiotics, and anticoagulants (Hudson and Nyman, 2011; Melloni et al, 2008; McCallum et al, 2013).

The findings of this review suggest that when investigating the prevalence in UK primary care, there is a need to assess kidney function using both CrCl-CG and MDRD equations, and to see how many patients would be missed if eGFR (MDRD) is used, that should have their treatment altered.

2.11.3.3 Risk to the patient if prescribing recommendations in RKF are not applied.

Inappropriate prescribing in RKF leads to a significantly increase in all-cause mortality of 40% (Breton et al, 2011), and increased risk of ADRs and hospital admissions (Helldén et al, 2009) in older people. The prevalence studies showing that older people have more inappropriate prescribing would suggest that they are more likely to be at increased risk of harm, and many of the studies reporting ADRs and hospital admission either had an older population, or reported high mean ages.

The drugs highlighted as causing harm in the studies are also similar to those implicated in the other review areas, for example:

- NSAIDs were frequently cited as causes of ADRs, including toxicity to the kidney, and hospital admission (Adams et al, 2011; Evans et al, 1995)
- Nitrofurantoin, both being ineffective as an antibiotic, and increased risk of hospitalisation from pulmonary ADRs, at low levels of kidney function (Geerts et al, 2013; Howard et al, 2013).
- Anticoagulants such as NOACs and heparin where there is an increased risk of bleeding if doses are not adjusted in RKF (Melloni et al, 2008; Cestac et al, 2003).

The risk of harm found in this review emphasises the need for further research into how to reduce inappropriate prescribing in RKF, particularly for older people.

2.11.3.4 Why do prescribers not implement prescribing recommendations?

No studies were found that aimed to explore the underlying behaviours and determinants of why the recommendations for prescribing when kidney function is reduced are not applied, and the barriers and enablers to improvement. There have been some good quality meta-syntheses and additional qualitative studies into inappropriate prescribing more generally (Anderson et al, 2014; Cullinan et al, 2014;

Slight et al, 2013). These studies have pointed to prescriber factors such as lack of problem awareness, fear of consequences of change, and personal ability. Also extrinsic factors such as the working environment, the feasibility of altering prescribing, and applying guidelines versus experience. The many factors involved were found to be complex and interdependent, with no one factor being dominant.

As there are important factors, such as the need for kidney function estimation calculation, there may be barriers and enablers to inappropriate prescribing that relate specifically to RKF and older people that should be explored before development of an intervention.

2.11.3.5 Are there resources to help with prescribing in RKF?

National and international policies and guidance have advised on management of kidney disease but do not cover dosing of drugs that need altering in the reduced kidney function of the older patient. The introduction of a different kidney function estimation equation for eGFR (MDRD) has not been clarified in the guidelines in relation to use for prescribing decisions, and for older people in particular (NICE CG182, 2014).

The BNF is a widely used and respected resource for prescribing, but the statement that eGFR gives similar results to creatinine clearance has been shown to not be the case for older people in this review. The BNF gives the recommendations for drug use in RKF in the drug monographs as eGFR, except for the NOACs where European guidance has stipulated that it needs to CrCl-CG; however, the figures are taken from the SPCs where CrCl-CG has been used. This scoping review would suggest that the BNF guidance is not adequately evidence-based because of the over-estimation of kidney function when eGFR is used in older people.

If the evidence can be strengthened on the impact in UK primary care, there might then be a case for the BNF to alter its guidance, and inform future national guidance on prescribing in RKF.

2.11.3.6 Have any interventions been evaluated to help prescribers apply recommendations for use of drugs in RKF?

The reporting of eGFR might have raised awareness of kidney disease but it has not improved prescribing in RKF. Evaluations of alerts and more sophisticated CDSSs have shown mixed results in a systematic review (Tawadrous et al 2011), but the studies that involved pharmacists in the intervention showed universally positive results. The Four RCTs found also showed positive effects:

- Dosing software improved ACEI/ARB prescribing in hypertension in older people (Erler et al, 2012).

- CDSS with an alert significantly improved prescribing in RKF (Field et al, 2009).

- Alerts to pharmacists significantly reduced errors for prescriptions in RKF (Bhardwaja et al, 2011).

- A pharmacist-led information technology intervention (PINCER) is an effective method for reducing a range of medication errors in general practices, including improvement of kidney function testing when taking an ACEI or diuretic (Avery et al, 2012).

None of the studies found aiming to improve inappropriate prescribing in RKF were based on theory or determinants of why recommendations were not applied, which might be a factor if the intervention was not addressing where the barriers are. A behaviour change theory based intervention for UK primary care needs to be developed and tested to reduce inappropriate prescribing.

2.11.4 Strengths and limitations

Use of a robust method for the scoping literature review made this study transparent and reproducible. A limitation is the reduced rigour having only one researcher with challenges such as uncertainty about which studies to include, variables to extract, and nature and extent of detail. These were sought to be reduced by searching on multiple databases, allowing re-evaluation of studies against the search criteria. Also, the systematic method was used to reduce the risk of bias and a one-sided view. Only studies published in English were included which may mean some relevant evidence may have been missed.

2.11.5 What this study adds to the literature

This study has been able to provide an update to the reviews such as Long et al (2004). With the international KDIGO guidelines and policy on CKD and AKI, there appears to now be greater interest in kidney disease and an increasing body of literature. Finding the gaps for future research confirmed the research plan to investigate prescribing for older people with RKF in UK primary care.

2.11.6 What this study adds to practice and policy

The review has highlighted that the guidelines and policy do not assess older people as a specialist group or provide guidance on use of drugs in reduced kidney function

and how to reduce risk of harm. A recent systematic examination of recommendations in twelve NICE clinical guidelines also concluded that drug-disease interactions with chronic kidney disease were common and that guideline developers should particularly consider whether chronic kidney disease is common in the target population (Dumbreck et al, 2015).

The BNF current guidance may not be evidence-based because of the over-estimation of kidney function when eGFR is used in older people. If the evidence can be strengthened on the impact in UK primary care, there might then be a case for the BNF to alter its guidance, and inform future national guidance on prescribing in RKF.

2.11.7 Progression and integration of methods and findings

The pilot study case-note review in Chapter 1 provided the key areas of literature review. Similar results to those found in GP practices in Bradford were found in studies from other countries, both for prevalence of inappropriate dosing, and discrepancies in the use of the different kidney function estimation equations for older people. As no other UK research was found in primary care, there was a need to test the findings in a wider population.

The scoping literature review has confirmed the research plan, and provided examples of methods and analyses, to:

- Study the extent of not applying recommendations in a larger population in UK primary care.
- Investigate the extent to which kidney function is tested for older people prescribed drugs that are affected by RKF.
- Explore why prescribers are not applying the recommendations in UK primary care, so that development of an intervention can address barriers and enablers and so be more likely to be effective.

2.12 Conclusion

The prescribing for the older patient with reduced kidney function does not always follow the recommendations and this can lead to an increased risk of ADRs and hospital admissions. The introduction of the nationally reported eGFR as a kidney function estimation did not improve prescribing in RKF, and its use overestimates the level of kidney function for older people meaning that they are at increased risk of harm. Gaps in the literature have been identified and research is needed to investigate prescribing for older people with RKF in UK primary care.

'The use of medications in older patients is arguably the single most important health care intervention in the industrialized world.'

J. Avorn, 2010

3 Chapter 3: A cross-sectional survey of prescribing data to investigate whether recommendations for prescribing are applied for older people across a PCT population

3.1 Background

A quarter of older patients with a documented reduced kidney function (RKF) were found to be taking drugs that were not recommended, in the small localised case-note review (Chapter 1). The scoping literature review (Chapter 2) found no other prevalence studies on prescribing for older people with RKF in UK primary care. Studies based in hospitals, and in other countries, suggest that recommendations in RKF are often not applied, with increased risk of harm and hospital admission.

This study aimed to test the case-note review findings in a wider population in UK primary care by quantifying inappropriate prescribing in a representative sample of drugs that require kidney function assessment prescribed for people aged 65 years and older.

3.2 Study question and objectives

Study question

Are drugs, that require kidney function assessment, prescribed according to recommendations for use in reduced kidney function for people aged 65 years and older across a Primary Care Trust (PCT) population?

Objectives

Primary objective:

- To assess the prevalence of a representative sample of drugs that require kidney function assessment for patients aged 65 years and over where the kidney function is too low for recommended use.

Secondary objectives:

- To assess whether a kidney function estimate was on the patient record where drugs that require kidney function assessment are prescribed.

- Whether using eGFR (MDRD equation) or CrCl-CG (Cockcroft Gault equation) would alter dosing decisions.

- Whether age is a factor in having a kidney function estimate too low for recommended use of drugs that require kidney function assessment.

3.3 Methodology

Drugs, age, and parameters related to kidney function needed to be investigated to give an indication of the extent to which drugs are prescribed outside recommendations for use RKF in primary care. A quantitative strategy was required to examine the relationships between and among the variables (Cresswell, 2009). As the intention was to test the findings from the case-note review in a wider population, an option might have been to extend that study. However,

- Case-note reviews are a lengthy process.
- GP practices would need to give consent to be included in a service evaluation beyond the usual workplace, and individual patients would need to give consent to allow their medical record to be accessed.
- Repeating the method would not allow a more detailed statistical analysis.

A cross-sectional survey design would allow a 'snap-shot' rapid investigation at a single moment in time in a larger sample. To allow the inclusion of large numbers of prescribing data, it was proposed to do the data collection by a structured record interrogation (Fink, 2002) for all people aged 65 years and older in the PCT population. Use of variables derived from the case-note review would allow the findings to be investigated further. Inclusion of all four categories (see below) of inappropriate drug use in RKF would explore any differences, and ensure the results were more likely to be generalisable, i.e.:

- Drugs to avoid in RKF
- Dose reduction required in RKF
- Drugs that are ineffective in RKF
- Drugs requiring caution as they are known to frequently cause adverse drug reactions (ADRs) in RKF.

Investigation of prescribing where there had never been a kidney function test done, or where there was not a recent check, would address one of the limitations of the case-note review study. Kidney function can alter over time, and as a result of disease, so a recent test should be available when making drug choice and dosing decisions for drugs affected by level of kidney function.

3.4   Study design

3.4.1   Setting

The former Bradford & Airedale Primary Care Trust (PCT) area was the setting for the prescribing data survey run in 2011. PCTs were part of the NHS in England from 2001 to 2013. They were large administrative bodies, responsible for commissioning primary, community and secondary health services from providers. Over 80% of all NHS funding went to PCTs (Department of Health, 2012).

The health of the people in Bradford is mixed, and deprivation higher, compared with the England average. Life expectancy for both men and women is lower (men: 76.6 years compared to 78.6 years, range 73.6 - 85.1 years; and women: 80.8 years compared to 82.6 years England average, range 79.1 - 89.8 years) (Public Health England, 2012). The 2011 Health Profile (Table 18) also shows the Bradford population is younger than the England & Wales average with fewer people aged 65 years and older (13% vs 16%), and 85 years and older (1.8% vs 2.2%), for both males and females (Office for National Statistics, 2011).

	whole population		65yrs and older			85yrs and older			
	England & Wales	Bradford	England & Wales		Bradford		England & Wales		Bradford	
all	53,012,456	522,452	8,660,529	16%	69,392	13%	1,180,128	2.2%	9,604	1.8%
male	26,069,148	257,132	3,844,839	15%	29,984	12%	383,568	1.5%	3,011	1.2%
female	26,943,308	265,320	4,815,690	18%	39,408	15%	796,560	3.0%	6,593	2.5%

Table 18: **Census 2011 population statistics for Bradford and England & Wales (Office for National Statistics, 2011).**

3.4.2   Drug choice

Two drugs, or drug classes, were identified from each of the four categories of inappropriate prescribing in RKF, i.e. for:

- Drugs to avoid in RKF
- Dose reduction required in RKF
- Drugs that are ineffective in RKF
- Drugs requiring caution as they are known to frequently cause adverse drug reactions (ADRs) in RKF.

The eight choices of drugs were based on the most frequently prescribed outside the recommendations in the case-note review, the strength of the evidence base, the impact on patients, and expert advice from a renal physician, geriatrician, hospital renal pharmacist, and an antibiotics expert pharmacist. The experts made their

judgement independently based on their experience. The evidence sources included the standard recommendations for use of drugs in RKF, such as the Summary of Product Characteristics (SPC) and British National Formulary (BNF). The basis for the drug choices are summarised in Table 19, and discussed in more detail below.

recommendation in RKF	drug	% prescribed inappropriately in the case-note review	recommendation in respected national resource	references highlighting inappropriate prescribing	comments from experts
avoid	alendronic acid	4.0	avoid if CrCl<35ml/min	Khanal et al,(2015). Breton et al (2011).	Agreed to be included.
	metformin	2.2	avoid if CrCl<30ml/min	Breton et al (2011) Khanal et al (2015) Schmidt-Mende et al (2012)	Suggested by a renal physician and a geriatrician as they see admissions to hospital caused by metformin in RKF.
reduce the dose	simvastatin	8.8	maximum dose 10mg if CrCl<30ml/min	Breton et al (2011)	Agreed to be included as a widely used drug with an alternative available.
	gabapentin and pregabalin	0.2	table of reduced doses at specified levels of CrCl	Breton et al (2011)	Added at the suggestion of the renal pharmacist because of frequent side effects seen in the renal unit.
ineffective	thiazides	17.0	ineffective at CrCl<30ml/min	Howard et al (2003)	Agreed to be included.
	nitrofurantoin	0.2 (on repeat)	ineffective at CrCl<45ml/min	Farag et al (2014) Howard and Wood (2013) Geerts et al (2013)	Added after discussion with a pharmacist with expertise in antibiotics.
caution in RKF	NSAIDs on repeat	1.7	caution in RKF	Guthrie et al (2011) Howard et al (2003) Evans et al (1995) Ingrasciotta et al (2014)	NSAIDs affect all stages of kidney function and are frequently a cause of hospital admission.
	ACEIs and ARBs	26.0	caution in RKF	Khanal et al (2015) Breton et al (2011) Schmidt-Mende et al (2012) Handler et al (2014)	Although ACEIs and ARBs are used in renal disease, they can also be nephrotoxic so the consultant experts suggested inclusion.

Abbreviations: ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; CrCl: creatinine clearance; NSAID: non-steroidal anti-inflammatory; RKF: reduced kidney function.

Table 19: Choices of drugs and drug classes to investigate in the cross-sectional survey.

3.4.2.1   Drugs to avoid in RKF

Alendronic acid is a bisphosphonate used to reduce the risk of bone fractures. The SPC states that it should be '*avoided if CrCl<35ml/min due to lack of experience'* which implies that there is no evidence base to support the use in low kidney function, although it also states that '*somewhat greater accumulation of alendronic acid in bone might be expected in patients with impaired renal function.*' The terminal half-life

exceeds 10 years so once taken up in the bone it is only eliminated extremely slowly, if at all.

a) Findings from the case-note review

Alendronic acid was the second most frequent drug found prescribed inappropriately in the case-note review with 24 patients, in the cohort of 594 (4%), found with a kidney function too low for recommended use (see Appendix 2, 8.2).

b) The evidence base

The evidence for restricted use in RKF has been described as 'not robust' by Courtney and Maxwell (2009). They state that initial safety issues were raised in the mid-1980s with reports of bisphosphonate accumulation in the kidneys of rodents. Later it was recognised that clinically significant renal failure can follow the rapid intravenous administration of bisphosphonates in humans. This information, together with the knowledge that approximately 50% of oral administered bisphosphonate is excreted by the kidney, led to the exclusion of persons with raised serum creatinine values from clinical trials. Cunningham (2007) found that individuals with CKD stage 2–4 (i.e. eGFR ≥15ml/min/1.73m^2) did not show evidence of increased toxicity or adverse effect. In patients with stage 5 CKD it has been suggested that reducing the dosage to half for post-menopausal osteoporosis seems reasonable from known bisphosphonate pharmacokinetics (Miller, 2005).

Alendronic acid was cited as one of the top five drugs prescribed inappropriately for older people in the Australian primary care prevalence study (Khanal et al, 2015); in 16.3% of 543 patients alendronic acid would be contra-indicated because of the reduced level of kidney function. The large, high quality, multi-centre, prospective cohort, French primary care study by Breton et al (2011) reported bisphosphonates as a group where they found 14% were prescribed inappropriately.

c) The impact for patients

Europe-wide reviews of bisphosphonates have been carried out since 2008 and have been recently summarised by the MHRA (MHRA, 2014). These include a low but increased risk of atrial fibrillation for zoledronic acid, pamidronate, and possibly for alendronate, that alendronic acid use is associated with an increased risk of atypical stress fractures of the proximal femoral shaft and a warning was subsequently added to alendronic acid product information, and that renal toxicity is a recognised adverse reaction associated with intravenous bisphosphonates.

d) Expert advice

The expert advisors independently agreed the inclusion of alendronic acid for this study.

Metformin is an anti-diabetic drug. The NICE recommendation is to avoid use of metformin at eGFR <30ml/min/1.73m^2 (NICE NG28, 2015). When kidney function is impaired, clearance of metformin is decreased and the elimination half-life prolonged, leading to increased levels of metformin in plasma.

For older people there is the specific recommendation in the SPC that '*due to the potential for decreased renal function in elderly subjects, the metformin dosage should be adjusted based on renal function. Regular assessment of renal function is necessary*'. It also stipulates that kidney function needs testing regularly at least 2-4 times a year in elderly subjects (estimated from serum creatinine using the Cockcroft-Gault formula). On elimination, renal clearance of metformin is stated as >400 ml/min, indicating that metformin is eliminated by glomerular filtration and tubular secretion. When kidney function is impaired, the clearance though the kidney is decreased in proportion to that of creatinine and so the elimination half-life is prolonged, leading to increased levels of metformin in plasma.

a) Findings from the case-note review

Thirteen patients (2.2%) were found where kidney function was too low for recommended use, or the dose needed review, and so was in the top five drugs that were not recommended for use because of RKF or the dose needed review.

b) The evidence base

Metformin was frequently cited in the studies in primary care found in the scoping review as being prescribed to patients when contra-indicated because of RKF, 15.3% of metformin prescribing in France (Breton et al, 2011), 17.8% in Australia (Khanal et al, 2015), and 8.4% in Sweden (Schmidt-Mende, 2012).

c) The impact for patients

Lactic acidosis is a metabolic complication that can occur due to metformin accumulation and occurs primarily in diabetic patients with impaired kidney function or acute worsening of kidney function (SPC). It is very rare, but is serious with a high mortality rate in the absence of prompt treatment.

d) Expert advice

Metformin was independently suggested for inclusion in this study by the renal physician and the geriatrician as they experienced patients admitted to hospital with lactic acidosis from use of metformin in RKF.

3.4.2.2   Dose reduction required in RKF

Simvastatin is widely used to reduce cholesterol levels, and in 2011 was the 'statin' of choice in Bradford. The SPC states that '*in patients with severe renal insufficiency (creatinine clearance <30 ml/min), dosages above 10 mg/day should be carefully considered and, if deemed necessary, implemented cautiously'*.

a) Findings from the case-note review

Simvastatin was the highest frequency single drug (x52, 8.8%) found to be prescribed outside the recommendations in the case-note review (see table Appendix 2, 8.2).

b) The evidence base

In a Personal Communication by S Wood to Merck Sharp & Dohme (12/10/11), the drug company stated that the dose reduction recommendation is based on a comparator statin, lovastatin, where the 'area under the plasma concentration-time curve' (AUC) for total and active HMG-CoA reductase inhibitory activity was 2 to 3 times higher in patients with RKF (mean CrCl 24ml/min, range 12-39ml/min) than in controls (Quérin et al, 1991).

An MHRA Drug Safety Update on dose limitations for simvastatin with interacting drugs found that concurrent use of drugs such as amlodipine with simvastatin causes a significant increase in blood levels of simvastatin which is associated with an increased risk of myopathy and/or rhabdomyolysis (MHRA, 2012). Studies have found that after 10 days of amlodipine (10 mg), the AUC of simvastatin and simvastatin acid following a single dose of simvastatin 80 mg increased by 1.58- and 1.77- fold respectively, compared with that following a single dose of simvastatin 80 mg without prior amlodipine administration (Merck, Sharp & Dohme, 1991). The fact that the MHRA needed to issue a Drug Safety Alert, and implement the changes in the dose requirements for simvastatin based on a nearly doubling of the AUC with an interacting drug, would lend weight to the fact that increases in AUC of 2-3 times in RKF should be taken seriously and could be increasing risk of harm for patients.

The French primary care study found that 3.8% of all statins needed dose adjustment (Breton et al, 2011).

c) The impact for patients

Increased blood levels of simvastatin are associated with an increased risk of myopathy and/or rhabdomyolysis (SPC). As the dose of simvastatin can be reduced when kidney function is low, and there is the option to switch to an alternative statin, atorvastatin, which does not need dose changes in RKF, any impact for patients can be avoided.

d) Expert advice

The expert advisors independently agreed the inclusion of simvastatin for this study.

Gabapentin and pregabalin SPCs state that they are eliminated solely though the kidney and that in older patients, and in patients with impaired kidney function, the plasma clearance is reduced. The elimination-rate constant, plasma clearance, and renal clearance are directly proportional to creatinine clearance.

The recommendations for use of gabapentin in RKF in the SPC show doses need altering at different levels of kidney function (Table 20). The SPC for pregabalin specifically details that the dose reduction in patients with compromised renal function must be individualised according to creatinine clearance (CrCl), as indicated in Table 21, that should be determined using the Cockcroft & Gault formula; the formula is provided in the SPC to be very clear about how the estimate should be calculated.

Kidney function (CrCl)	Total daily dose (mg)
80ml/min or higher	900-3600
50-79 ml/min	600-1800
30-49 ml/min	300-900
15- 29 ml/min	150-600 (150mg as 300mg alt days)
<15 ml/min	150-300

Table 20: **Dose recommendations in RKF for gabapentin (SPC)**

CrCl as calculated by Cockcroft & Gault	Starting dose (total mg/day)	Max dose (total mg/day	Dose regimen
60 ml/min and over	150	600	bd or tds
30-59 ml/min	75	300	bd or tds
15-29 ml/min	25-50	150	od or bd
<15 ml/min	25	75	od

Table 21: **Dose recommendations in RKF for pregabalin (SPC)**

The SPC for pregabalin states that clearance tends to decrease with increasing age and that this is consistent with decreases in creatinine clearance associated with

increasing age. Reduction of pregabalin dose may be required in patients who have age related compromised kidney function.

a) Findings from the case-note review

Only one patient in the case-note review had been found to be on gabapentin at a dose too high for their kidney function, and no patients on pregabalin, so they were not initially highlighted as drugs for investigation in the survey.

b) The evidence base

Breton et al (2011) reported that in 5.6% of antiepileptics in the French primary care study required dose adjustment because of RKF had not been done, which included gabapentin and pregabalin.

c) The impact for patients

Somnolence, dizziness, ataxia, and fatigue are described in the SPC as very common (≥ 1 in 10), and many 'common' ADRs are listed, including psychiatric, nervous system, skin and gastrointestinal reactions (≥ 1/100). Although used for epilepsy, they have increasingly been prescribed for neuropathic pain.

NHS England (2014) analysed electronic prescribing data for primary care for prescribing of gabapentin and pregabalin, and in 2013 the total use in England of both was 8.2 million prescriptions; this represents a 46% rise in prescribing of gabapentin and 53% rise in pregabalin prescribing since 2011. The increase in use of these drugs in primary suggests an increase in risk for patients if kidney function is not assessed and doses altered accordingly.

d) Expert advice

Gabapentin and pregabalin were suggested for inclusion on the advice of the renal pharmacist because ADRs are frequent and often related to dose and kidney function level.

3.4.2.3 Ineffective in RKF

Thiazides are usually prescribed for hypertension, but they require an adequate level of kidney function to work and they are ineffective at CrCl <30ml/min (BNF70, 2015). In the SPC for indapamide, for example, it states that in severe renal failure (CrCl <30 ml/min), treatment is contraindicated and that thiazides are fully effective only when kidney function is normal or only minimally impaired.

a) Findings from the case-note review

Thiazides were the third most implicated class of drugs in the case-note review with 17% found to be prescribed when kidney function was <30ml/min (see table Appendix 2, 8.2).

b) The evidence base

Howard et al (2003) investigated reasons for preventable drug related admissions to a medical admissions unit in the UK. Thiazides were one of the drug classes most frequently associated with preventable drug related admissions due to monitoring problems. They cite failure to monitor kidney function, fluid balance and electrolytes as a factor in ADRs such as over diuresis causing dehydration and renal failure.

c) The impact for patients

The risk for patients is from both under-treatment as well as increased risk of side effects such as electrolyte disturbance.

d) Expert advice

The expert advisors independently agreed the inclusion of thiazides for this study.

Nitrofurantoin is used to treat urinary tract infection (UTI) and is most often prescribed as a short course. The SPC and BNF (2010) at the time of the survey stated that nitrofurantoin is ineffective if CrCl is less than 60ml/min as there would not be an adequate concentration in the urine to be active against infection. The Renal Drug Handbook 2nd Edition (Ashley & Currie, 2007) also stated that nitrofurantoin was contra-indicated at CrCl <60ml/min.

a) Findings from the case-note review

The case-note review only reviewed long term medication and so did not assess the usual acute use of nitrofurantoin in RKF. However, one patient was found who was taking regular prophylactic nitrofurantoin but kidney function was lower than recommended.

b) The evidence base

The recommendation for prescribing in RKF had originally been based on inadequate urinary concentration at <60ml/min found in a small study of eleven subjects with normal kidney function and six with renal insufficiency (Felts et al, 1971). In 2014 the MHRA published a Drug Safety Update to change the recommendations to be contraindicated at eGFR <45 ml/min/1.73m^2, to consider checking kidney function when choosing to treat with nitrofurantoin, especially in the elderly, and to closely monitor for signs of pulmonary, hepatic, neurological, haematological, and gastrointestinal side effects during treatment. The revision in recommendations was based on two studies. Oplinger and Andrews (2013) suggested the limited data available would support use of nitrofurantoin in CrCl of 40ml/min or higher. Geerts et al (2013) found that nitrofurantoin treatment was not associated with a higher risk of ineffectiveness in women with a moderately reduced kidney function (30-50

ml/min/1.73 m²). The analysis of the survey data was altered to reflect the change in recommendation.

Farag et al (2014) investigated antibiotic use in RKF for older people in Canada; they noted that nitrofurantoin had been prescribed when contra-indicated 169 times in the 1,464 antibiotics prescriptions studied.

The addition of a drug that is mostly acute use as a short course addresses one of the limitations in the case-note review where only repeat medications were assessed.

c) The impact for patients

ADRs are more likely in RKF and an infection may not be treated. A small pilot audit on the effectiveness of nitrofurantoin suggested that older patients with reduced kidney function were more likely to need a follow up course of an alternative antibiotic if the kidney function was low (Howard & Wood, 2012). Geerts et al (2013) found a significant association between renal impairment (<50 ml/min/1.73 m²) and pulmonary adverse events leading to hospitalisation.

d) Expert advice

The antibiotics expert pharmacist suggested inclusion as use was increasing with the national aim to reduce methicillin-resistant staphylococcus aureus (MRSA) and clostridium difficile infection after antibiotic use (NICE KTT9, 2016). However, the recommendations were that nitrofurantoin was ineffective at CrCl <60ml/min which would exclude many older people, and there was interest in investigating the numbers of patients that would be affected.

3.4.2.4 Caution because known to frequently cause ADRs in RKF

Non-steroidal anti-inflammatories (NSAIDs) reduce pain and inflammation, but their effect on prostaglandin synthesis leads to many side effects including the inhibition of renal prostaglandin synthesis and affect all aspects of the function of the kidney (Ashley and Morlidge, 2008; Ashley and Currie, 2014). If the NSAID is also eliminated via the kidney, such as naproxen (95%), then the adverse effect can be compounded as the blood levels are increased. The BNF states in each drug monograph for NSAIDs:

> '*Avoid if possible or use with caution in patients with renal impairment; the lowest effective dose should be used for the shortest possible duration, and renal function should be monitored. Sodium and water retention may occur and renal function may deteriorate, possibly leading to renal failure*' (BNF70, 2015, pp.917-937).

NSAIDs are specifically mentioned in the NICE CKD and AKI guidance (NICE CG182, 2014; CG169, 2013) including chronic use of NSAIDs as a risk factor for progression of CKD and the requirement for monitoring kidney function at least annually in people prescribed drugs known to be nephrotoxic, such as NSAIDs.

The BNF guidance to avoid in severe renal impairment (defined in previous BNFs as <30ml/min, BNF55, 2008) informed the decision to set this level as the marker.

a) Findings from the case-note review

Four patients (1.7%) in the case-note review had an NSAID on their repeat medication list when their kidney function was <30ml/min. A further 6 had a topical NSAID gel.

b) The evidence base

NSAIDs are frequently cited in the research literature as being prescribed inappropriately causing ADRs and hospital admission. Wiffen et al (2002) reported that NSAIDs were responsible for between 60% and 70% of all ADRs leading to hospital admission, or causing ADRs within a hospital episode. NSAIDs were the most commonly prescribed contra-indicated nephrotoxic drugs prescribed to CKD patients in an Italian primary care study, 56.3% had at least one prescription for an NSAID, a third were treated for over 90 days, and 16.5% for greater than 6 months (Ingrasciotta et al, 2014). Guthrie et al (2011) found that 8.2% of patients aged 65 years and over with a glomerular filtration rate <60 ml/min received a 'high risk prescription' of an NSAID.

c) The impact for patients

NSAIDs were a drug class most frequently associated with preventable drug related admission in the UK due to prescribing problems including not monitoring kidney function in the Howard et al study (2003), and Evans et al (1995) showed that there was an approximate doubling of the risk of hospitalisation with acute renal failure with use of oral NSAIDs.

d) Expert advice

The expert advisors independently agreed the inclusion of NSAIDs for this study.

Angiotensin converting enzyme inhibitors (ACEIs) and angiotensin-II receptor blockers (ARBs) affect the renin-angiotensin hormone system which controls blood pressure and the volume of fluids in the body. Drugs that have an inhibitory action on the renin-angiotensin hormone system (including ACEIs and ARBs) are used to treat high blood pressure and congestive heart failure. The BNF (BNF70, 2015) details that, although ACEI and ARBs are prescribed in kidney disease, they can be nephrotoxic and higher than normal plasma levels can cause further renal impairment and set up a

cycle leading to acute kidney injury. It states that kidney function and electrolytes should be checked before starting ACEIs or ARBs, or increasing the dose, and monitored during treatment.

a) Findings from the case-note review

ACEI/ARBs were inappropriately dosed, or needing review, in 26% of patients in the case-note review. They were also involved in two cases of acute kidney injury noted whilst doing the review, one causing hospitalisation.

b) The evidence base

Prevalence studies found in the literature review reported ACEI and ARBs frequently inappropriately prescribed. Perindopril was the top drug prescribed outside recommendations in the Australian retrospective survey study at 44.1%, and olmesartan was also one of the top five drugs contra-indicated in older people with RKF (Khanal et al, 2015). Breton et al (2011) found 2.9% of their older study population were taking drugs affecting the renin-angiotensin system that were contra-indicated or needed the dose adjusting. Schmidt-Mende et al (2012) showed that enalapril and candesartan were particularly notable for inappropriate prescribing. Handler et al (2014) found that the most common drugs causing AKI alerts to be triggered were ACEI/ ARBs.

c) The impact for patients

Some ACEIs are mostly excreted via the kidney, such as lisinopril and enalapril. The latter has an 'AUC' eight times normal at CrCl of <30ml/min (SPC), and so a patient with a kidney function level of <30ml/min given a 'usual maintenance' dose of 20mg a day would be getting the equivalent of 160mg and be at very high risk of serious adverse effects, including nephrotoxicity, and thus making kidney function even worse.

Renal impairment, hyperkalaemia, and hypotension are amongst many side effects that are more common in patients with RKF (SPC). As cited in the studies found in the literature review, and in the case-note review, inappropriate prescribing in RKF causes ADRs and increased risk of hospitalisation.

d) Expert advice

The renal physician and geriatrician suggested that ACEI/ARBs should be included in the survey as patients are frequently hospitalised as a result of prescribing in RKF causing AKI.

3.4.3 Variables

'Patient drug event' definition

A 'patient drug event' is when a patient has had at least one prescription for the study drug. For the 7 drugs that were prescribed for regular use, a 'patient drug event' was defined as the drug being on the repeat medication list at the time of the survey. For 1 drug (nitrofurantoin), as a drug most usually prescribed acutely as a short course, 'patient drug event' was defined as the drug was prescribed at least once in the previous 12 months.

Variables

The variables for data collection were:

- Age – actual age at time of search.
- Gender.
- Weight (kg) and date last recorded.
- Serum creatinine (SrCr) (micromol/l) and date last recorded.
- eGFR (ml/min/1.73m^2) and date last recorded.
- No eGFR on the record.

The date 'last recorded' would be what the prescriber would have available when making the decision whether to prescribe or reauthorise after review. It would also allow assessment for those who have a 'recent' estimate on the record, defined as within the last 15 months as used by the primary care general practice Quality Outcomes Framework (QOF) (Health & Social Care Information Centre, 2015).

For each drug surveyed, every 'patient drug event' had eGFR and CrCl-CG (using both actual weight and ideal body weight) kidney function estimates recorded, as detailed below. A reminder of the kidney function estimate definitions and abbreviations is provided in Table 1 (Page 22) with the abbreviations table to give an easy reference for this chapter.

- eGFR: recorded from the patient record. Even though the literature review found evidence that CrCl-CG should be used in prescribing decisions for older people, eGFR is reported by pathology and so widely available. Inclusion allows assessment of the proportion of patients that might be missed if eGFR was used instead of CrCl-CG.

- CrCl-CG AW: creatinine clearance calculated using actual weight, SrCr and age variables. The BNF stipulates using ideal body weight (IBW) in the Cockcroft Gault equation as a measure of muscle mass (BNF70, 2015). However, at least one of the primary care patient record systems (SystmOne)

used actual weight in the renal calculator for CrCl-CG at the time of the survey (the SystmOne renal calculator has now been revised to use IBW). Inclusion allows assessment of the proportion of patients that might be missed if actual weight was used instead of IBW.

- CrCl-CG IBW: creatinine clearance calculated using ideal body weight (or actual if lower), SrCr and age variables. An average ideal body weight of 60kg for females and 70kg for males was used as ideal body weight or lean body weight was not available to search. This is a reasonable assumption to make as the highest weights are reduced to a level more likely to approximate the lean body weight and give an indication of muscle mass (rather than body fat). CrCl-CG IBW is included as the kidney function calculation recommended by the BNF for 'toxic drugs with small safety margins' (BNF70, 2015).

Kidney function varies widely between individuals but does generally decline with age, whether that is related to disease or senescence (Glassock and Winearis, 2009). It would be anticipated that the problem of inadequate kidney function for prescribing of renally excreted drugs would be greater for older people. Age was included to see the effect of increased age on whether each drug would be appropriately prescribed. Age bands were used to enable comparison of the 'younger old' with the 'oldest old'. The Office for National Statistics (2011) starts the old age band at 65 years, and the 'older old' band at 85 years. To give three older age bands for comparison, the data was analysed in the following age categories:

- 65 – 74 years.
- 75 – 84 years.
- 85 years and older.

By including a search for those with 'no eGFR' on the record ensured it was possible to calculate the total number of people taking each drug, and therefore the number of those who did not have any of the variables required to estimate their kidney function.

3.4.4 Sample inclusion criteria

The samples to be investigated were all 'patient drug events' for each of the included drugs prescribed for people aged 65 years and older in the PCT population.

Eight separate sample populations of 'patient drug events' for the following drugs were planned to be extracted for analysis:

- Alendronic acid on repeat prescription.
- Metformin on repeat prescription.
- Simvastatin on repeat prescription.
- Gabapentin and pregabalin on repeat prescription.
- Nitrofurantoin prescribed within the previous 12 months.
- A thiazide on repeat prescription.
- An NSAID on repeat prescription.
- An ACEI, or ARB on repeat prescription.

3.4.5 Method

3.4.5.1 Data extraction

Having defined the variables and drugs to investigate, the criteria that needed to be collected by the searches were discussed with a PCT data analyst to ensure they could be extracted from the prescribing data. All GP practices across the Bradford & Airedale PCT used the SystmOne patient record system and so the prescribing data searches only needed to be run on SystmOne. The PCT data analyst ran the required searches for each drug at the end of October 2011 resulting in an anonymised data set for each drug.

The anonymised data extracted was presented as an Excel workbook and forwarded to the research team for analysis. The first two data sheets were:

- Total population – age and gender patient count.
- Total number of patients aged ≥65 years with eGFR <60ml/min/1.73m^2.

Then three excel data sheets for each of the eight drugs or drug classes for people aged ≥65 years:

- Age, gender, weight and SrCr for calculation of CrCl (both using actual body weight (CrCl AW) and estimated ideal body weight or actual if lower (CrCl IBW)).
- eGFR.
- No eGFR in the last 15 months.

An assessment of missing data and outliers was then conducted:

- The searches used meant that only drug prescriptions where a kidney function test, or variables to calculate kidney function level, were extracted. An analysis was undertaken to find the number of 'patient drug events' for each drug that occurred when there was no kidney function estimate on the record. This would

indicate the number that were missing from the analyses, and how reliable the findings would be for the whole population.

- The data sheets were checked for any missing variable data. As the extraction was done using searches for the variables, missing variable data was unlikely. However, a missing data analysis was performed to confirm this (3.4.5.2).

- Outliers were examined in the data, and assessed whether they should be included in the final analysis. Kidney function can be good, even in old age, or it can be extremely low because of disease. A kidney function variable would only be excluded if it was assessed to be most likely to have been a recording error. For example, weight data that was found to be lower than possible for an adult was assessed, and the patient drug event removed before analysis.

3.4.5.2   Missing data analysis

In order to ensure that any missing variables were identified, the effect on the final analyses, and to flag up any potential for bias, a missing data analyses was performed. As it was intended that the statistical program SPSS would be used for the inferential analysis, it would be important to do a missing data analysis as the program may automatically remove cases with missing variables without deleting from the data set; this may be significant, especially if a dataset has a high percentage of values missing. Also statistical procedures such as regression analysis will not work as well, or at all, on a data set with missing values. As the aim is to make inferences about the entire target population, it is necessary to clarify that the cases included for inferential analysis are representative (Rubin et al, 2002).

By doing a missing data analysis, the extent and pattern can be clarified and an assessment can be made as to whether to omit everyone without complete data and do a complete case (or available case) analysis. When only a very few observations are missing there will be little effect, but when many are missing, omitting all patients without full data might result in a large proportion of the data being discarded, and the results may be biased unless the data are missing completely at random (Altman & Bland, 2007).

3.4.5.3   Descriptive analysis

The anonymised data was assessed by a descriptive analysis. Statistician advice was sought because of the non-linearity of the data, the possible linkages where different study drugs might be prescribed to the same patients, and to ensure the statistical analysis would give clarity to the large set of data.

As the data extraction was done for 'patient drug events' where all parameters were available, a 'complete case analysis' was undertaken. Data could only be analysed for drug events where a kidney function estimate was on the patient record. It is recognised that biases may occur as data was not missing completely randomly; the data is unknown for drug events where the patient had no kidney function estimate on their record.

A descriptive analysis using Excel was completed for each drug to organise and 'illuminate the data' and answer the objectives (Bowers, 2008) to give:

- Population statistics:
  - Total population in Bradford & Airedale PCT
  - Number aged ≥65 years, and in the age bands 65-74, 75-84, and ≥85 years.
  - Number aged ≥65 years, and in the age bands 65-74, 75-84, and ≥85 years for male and female.

- The numbers of people aged ≥65 years taking each of the study drugs in the Bradford & Airedale PCT population, and in the age bands 65-74, 75-84, and ≥85 years.

- The number of older people with a documented RKF in the population, defined as eGFR <60 ml/min/1.73m^2 for CKD (NICE CG182, 2014), in those aged ≥65 years, and in the age bands 65-74, 75-84, and ≥85 years. This would give an indication of the level of recorded CKD in the Bradford & Airedale PCT population and allow comparison with other areas. It is noted that not all people with CKD will have had an eGFR check. The missing data analysis (3.4.5.2) will be able to give an assessment of the number of people prescribed the drug but without an available kidney function level on their record.

Separately for each of the eight selected, representative, drugs:

- The number of 'patient drug events' where a recent kidney function was available but was too low for the recommended use.
- The number of 'patient drug events' that would be missed if eGFR or actual weight was used to calculate creatinine clearance (CrCl-CG AW) were used instead of ideal body weight (CrCl-CG IBW),
- A line plot charting the range of kidney function at each age level.
- An assessment of correlation between age and level of kidney function (see 3.4.5.4 for further details).

- A logistic regression analysis to explore the effect of older age on likelihood of having a kidney function too low for appropriate prescribing of the drug (see 3.4.5.5 for further details).

Kidney function estimates done within the previous 15 months were used for the final three analyses, rather than any test on the record, as this would be more accurate and ideally a recent test should be available to make drug use and dose decisions.

Any results from the data analyses that were unexpected, were checked against figures found in one large GP practice for corroboration.

3.4.5.4 Correlation analysis

Use of the Pearson's correlation analysis assumes that:

- The two variables are continuous.
- There is a linear relationship between the two variables.
- There are no significant outliers.
- The variables are approximately normally distributed.

The data extraction is for people aged 65 years and older and so there are a much larger number of the population in the lower older age categories than at the oldest ages and the data is likely to be skewed. There are also outliers in the kidney function data in this older population where a few have very high level of function, and a few have a very low function because of disease.

Spearman's rank correlation coefficient is appropriate when one or both variables are skewed or ordinal and is robust when extreme values are present (Bowers, 2008). The age variable in these analyses were skewed when tested using IBM SPSS 22.

A Spearman correlation was run for each drug on IBM SPSS 22 to determine the relationship between an individual's age and level of kidney function. Both variables are continuous, and the data was assessed to ensure there was a linear relationship between the variables.

Definitions for the results reported:

r = correlation coefficient (range -1 to +1)

n = number included for analysis

p = level of statistical significance

3.4.5.5 Inferential analysis

A logistic regression analysis was performed using IBM SPSS 21 to investigate whether the independent variable, age, predicts higher odds of having a kidney function estimate too low for recommended use of the investigation drug (the

dependent variable). The independent variable was investigated in three age bands: 65-74 years, 75-84 years and aged 85 years and older. The dependent variable is kidney function level in relation to the recommendations for use of the investigation drugs. The 75-84 years, and aged 85 years and older, age groups were compared to the 65-74 age group.

It was decided to use the kidney function estimates done within the previous 15 months, rather than any test on the record, however long ago it was done, as ideally a recent test should be available to make drug use and dose decisions. Fifteen months is a time period used by the primary care general practice Quality Outcomes Framework as cut off for what would be considered a time period when there should have been monitoring for clinical review (Health & Social Care Information Centre, 2015).

The 95% confidence interval (CI) were assessed to estimate the precision of the odds ratios. A large CI indicates a low level of precision of the odds ratio, whereas a small CI indicates a higher precision. If the CI overlaps the null value (=1 for this analysis), there cannot be confidence that the outcome will occur given the particular exposure.

This analysis does not address the possibility of confounding, where a non-casual association is observed between a given exposure and outcome is as a result of the influence of a third variable. The findings need to be interpreted with this in mind. Stratification and multiple regression techniques are two methods used to address confounding, and produce 'adjusted' odds ratios, but were not within the scope of this analysis.

3.4.6 Ethics and governance

Approval was granted from the PCT governance lead on 21/10/11 as a service evaluation (Letter of access: Appendix 5, 8.4). It was confirmed with the National Research Ethics Service on 4/11/11 that, as part of an audit, NHS ethics approval was not required (Appendix 6, 8.5). All data had been anonymised before being released for analysis and there was no GP practice or patient identification possible.

3.5 Results

70,900 Highlighted figures in the tables are those mentioned in the text, results or discussion.

3.5.1 Population statistics.

70,900 people in Bradford & Airedale PCT were aged 65 years and older, 12.9% of the 549,533 total population, and 1.8% were ≥85 years (Table 22).

	number	% of total population	male	% of total population	female	% of total population
total PCT population	549,533					
total aged ≥65yrs	70,900	12.9	30,953	5.6	39,947	7.3
total aged 65-74yrs	36,466	6.6	17,471	3.2	18,995	3.5
total aged 75-84yrs	24,711	4.5	10,431	1.9	14,280	2.6
total aged ≥ 85yrs	9,723	1.8	3,051	0.6	6,672	1.2

Table 22: Bradford & Airedale PCT study population statistics.

3.5.2 The numbers of people aged ≥65 years taking the study drugs.

At least 40% of the 70,900 study population were on one or more drugs affected by level of kidney function in this population with 39.9% of all ≥65 year olds prescribed an ACEI or ARB. Table 23 shows that the proportions of the population taking the study drugs ranged from the 39.9% taking an ACEI or ARB, to 2% on gabapentin or pregabalin, and are shown in Figure 14. The high number found taking ACEI/ARBs was checked with the number in one GP practice which had a similar percent and so corroborated the result as the level that wold be expected.

For those aged ≥85 years the range was from 1.9% on NSAIDs to 35.9% on ACEI/ARBs.

	number aged ≥65yrs	% of those aged ≥65yrs	aged 65-74yrs		aged 75-84yrs		aged ≥85yrs	
			number	% of those aged 65-74yrs	number	% of those aged 75-84yrs	number	% of those aged ≥85yrs
alendronic acid	4,230	6.0	1,471	4.0	1,827	7.4	932	9.6
metformin	6,436	9.1	3,594	9.9	2,365	9.6	480	4.9
simvastatin > 10mg	21,733	30.7	11,200	30.7	8,249	33.4	2,284	23.5
gabapentin or pregabalin	1,448	2.0	725	2.0	526	2.1	197	2.0
nitrofurantoin (acute)	3,489	4.9	1,356	3.7	1,322	5.3	811	8.3
a thiazide	12,098	17.1	5,993	16.4	4,662	18.9	1,443	14.8
NSAID on rpt	3,363	4.7	2,194	6.0	987	4.0	182	1.9
ACE/ARB	28,254	39.9	13,739	37.7	11,023	44.6	3,490	35.9

Abbreviations: ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; NSAID: non-steroidal anti-inflammatory; RKF: reduced kidney function.

Table 23: Numbers prescribed each of the cross-sectional survey drugs.
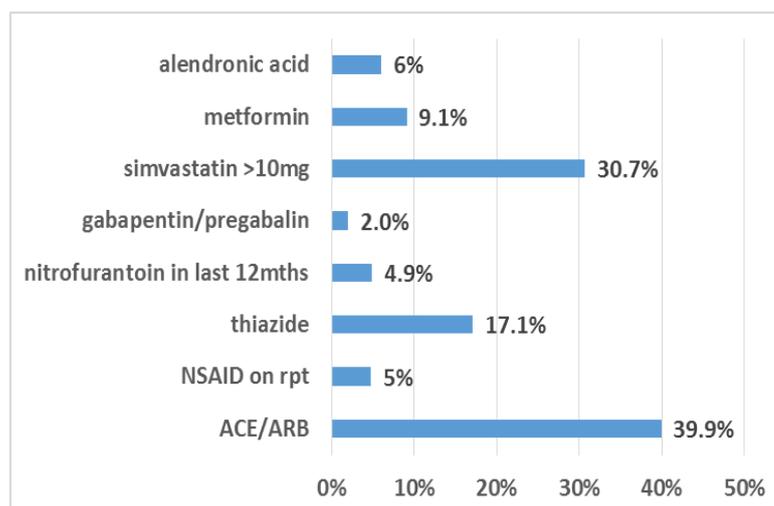
Abbreviations: ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; NSAID: non-steroidal anti-inflammatory; RKF: reduced kidney function.

Figure 14: The percentage of people aged ≥65 years prescribed each of the study drugs (from Table 23).

3.5.3 The level of documented RKF in the population.

Using the NICE CKD level of eGFR <60ml/min/1.73m^2, 25.9% of those aged ≥65 years, and 49.5% aged ≥85 years, had a documented reduced kidney function on their record (Table 24). More females than males had a lower kidney function in all three age bands, 17.1% vs 12.9% for the 65-74 years, 34.6% vs 30% for the 75-84 years, and for ≥85 years 51% of females and 46.4% of males had a reduced eGFR.

		number aged ≥65yrs	% of those aged ≥65yrs	aged 65-74yrs		aged 75-84yrs		aged ≥85yrs	
				number	% of those aged 65-74yrs	number	% of those aged 75-84yrs	number	% of those aged ≥85yrs
number with eGFR ≤60ml/min/1.73m^2	total	18,397	25.9	5,502	15.1	8,078	32.7	4,817	49.5
	male	6,811	22.0	2,262	12.9	3,132	30.0	1,417	46.4
	female	11,586	29.0	3,240	17.1	4,946	34.6	3,400	51.0

Table 24: Number of people aged ≥65 years with an eGFR <60ml/min/1.73m^2.

3.5.4 Missing data and outliers analysis

3.5.4.1 Missing data for age and gender

Virtually no ages or genders were missing from the data set. This is as expected as the GP patient record systems have age and gender as required fields.

3.5.4.2   Missing data for kidney function estimate calculation

Only 0.2% (metformin) to 9.7% (NSAIDs) of the patient drug events for each drug studied did not have an eGFR available on the patient record, and 0% (metformin) to 5.7% (NSAIDs) did not have the parameters to calculate CrCl-CG, i.e. age, gender, weight, and serum creatinine (Table 25).

Metformin at 2.8% to 17.5% (NSAIDs), did not have a recent eGFR in the previous 15 months and 2.4% to 21.9% did not have a recent SrCr on the record (weight was not included for a 'recent' value as ideal body weight was the BNF suggested variable; however, two thirds of cases did have a recent weight value on their record) (Table 25).

Figure 15 charts the percentage of patient drug events for the study drugs with no eGFR, or no eGFR in the previous 15 months.
The figures were similar for the ≥85 year olds but slightly higher at 1.5% - 19.8% for a recent eGFR and 2.5% - 20.9% for SrCr (Table 25).

The missing data analysis for patients who had a kidney function estimate in the previous fifteen months, has shown that approximately 10% of the data would not be used for the final analysis (9,911 out of 96,900).
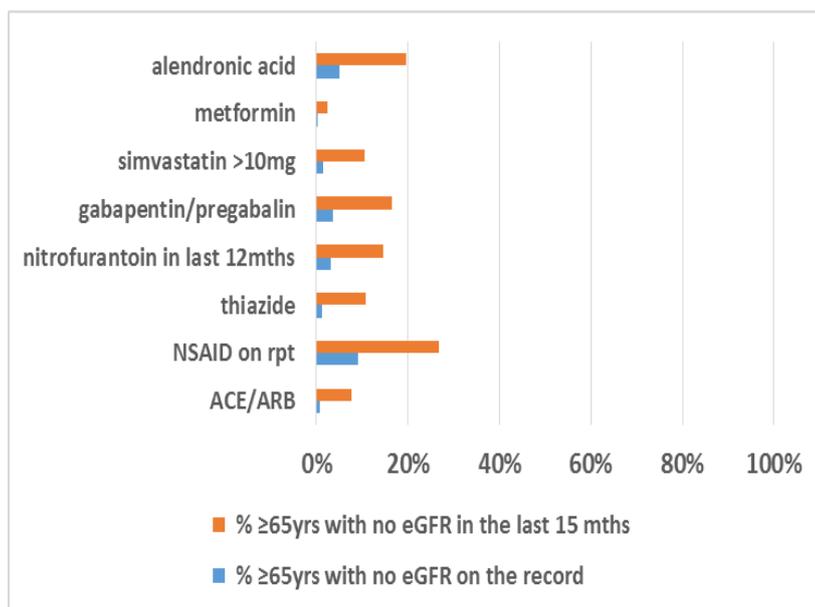
Abbreviations: ACE: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; eGFR: estimated glomerular filtration rate; NSAID: non-steroidal anti-inflammatory.

Figure 15: The percentage of 'patient drug events' for people aged ≥65 years with no eGFR on the record, or no eGFR in the last 15 months (from Table 25).

drug	aged ≥65yrs eGFR (ever)			aged ≥65yrs weight & SrCr (ever)			aged ≥65yrs eGFR (in last 15 mths)			aged ≥65yrs SrCr (in last 15 mths) and weight ever			aged ≥85yrs eGFR (in last 15 mths)			aged ≥85yrs SrCr (in last 15 mths) and weight ever		
	yes	"no"		yes	"no"		yes	"no"		yes	"no"		yes	"no"		yes	"no"	
alendronic acid	4,016	214	5.3	4,056	174	4.3	3,469	580	14.3	3,400	656	16.2	766	166	17.8	748	184	19.7
metformin	6,415	16	0.2	6,433	0	0.0	6,233	182	2.8	6,278	155	2.4	473	7	1.5	468	12	2.5
simvastatin >10mg	21,404	329	1.5	21,420	313	1.5	19,483	1,921	9.0	19,433	1,987	9.3	2,063	226	9.9	2,047	237	10.4
gabapentin or pregabalin	1,397	51	3.7	1,387	61	4.4	1,233	164	11.8	1,387	176	12.7	166	31	15.7	162	36	18.3
nitrofurantoin	3,383	106	3.1	3,385	104	3.1	3,013	370	10.9	2,979	406	12.0	754	57	7.0	737	74	9.1
thiazides	11,936	162	1.4	11,907	191	1.6	10,876	1,060	8.9	10,807	1,100	9.2	1,267	176	12.2	1,246	197	13.7
NSAIDs	3,054	309	9.7	3,181	182	5.7	2,498	556	17.5	2,483	698	21.9	145	36	19.8	144	38	20.9
ACE/ARB	28,063	191	0.7	27,875	379	1.4	26,222	1,841	6.6	26,117	1,758	6.3	3,215	275	7.9	3,168	322	9.2

Abbreviations: ACE: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; eGFR: estimated glomerular filtration rate; NSAID: non-steroidal anti-inflammatory; RKF: reduced kidney function; SrCr: serum creatinine.

Table 25: Kidney function variables available on the patient record for each of the study drugs ever, and in the previous 15 months, for age ≥65 years and ≥85 year

drug	aged 65yrs and older				aged 65-74yrs				aged 75-84yrs				aged 85yrs and older			
	total	KF < recmd'd	%	CI (±)	total	KF < recmd'd	%	CI (±)	total	KF < recmd'd	%	CI (±)	total	KF < recmd'd	%	CI (±)
alendronic acid	3,400	804	23.6	0.04	1,120	49	4.4	0.01	1,532	342	22.3	0.02	748	413	55.2	0.07
metformin	6,276	267	4.3	0.03	3,491	30	0.9	0.0005	2,319	124	5.3	0.004	466	113	24.2	0.08
simvastatin > 10mg	19,434	1,465	7.5	0.01	9,894	167	1.7	0.0003	7,494	643	8.6	0.002	2,046	655	32.0	0.02
gabapentin or pregabalin	1,209	132	10.9	0.1	598	43	7.2	0.02	450	56	12.4	0.05	161	33	20.5	0.2
nitrofurantoin	3,185	1,262	39.6	0.04	1,206	141	11.7	0.02	1,242	535	43.1	0.04	737	586	79.5	0.04
thiazide	10,805	797	7.4	0.02	5,371	62	1.2	0.0004	4,189	303	7.2	0.003	1,245	432	34.7	0.04
NSAID	2,483	86	3.5	0.08	1,577	8	0.5	0.001	762	36	4.7	0.01	144	42	29.2	0.3
ACE/ARB	26,109	2,521	9.7	0.01	12,663	288	2.3	0.0004	10,280	1,062	10.3	0.002	3,166	1,171	37.0	0.01

Abbreviations: ACE: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; CI: confidence intervals; KF<recmdd: kidney function less than recommended; NSAID: non-steroidal anti-inflammatory.

Table 26: Number of drugs prescribed for people aged ≥65 years with a kidney function estimate (CrCl-CG IBW) in the previous 15 months too low for recommended use.

3.5.4.3 Outliers

No eGFR or SrCr values were considered to be errors as both the lower and higher values were possible when kidney function is very low or is normal. Only five weight values across all the 79,644 values extracted for the eight drugs were assessed as likely to be a recording error as they were too low to be an adult weight. The five 'patient drug events' were removed from the analysis, but such a low level in the whole study population would not bias the study findings.

3.5.5 Analysis of the eight sample drugs

The data for each drug was collected separately without data linkage. The statistical analysis could therefore only be conducted for each drug individually. Tables 26 and 27 are used to list the data that will then be used in the individual drug sections.

Table 26 shows the number of drugs prescribed in the study population (people aged ≥65 years) with a kidney function estimate (CrCl-CG IBW) in the previous 15 months too low for recommended use. Table 27 gives the results comparing the effect of using the recommended equation for prescribing decisions (i.e. CrCl-CG IBW) with using actual weight in the equation (CrCl-CG AW) or using the nationally reported eGFR. The data is presented as the number of patients prescribed the drug but who have a kidney function too low and would be missed if CrCl-CG IBW was not used.

The data is presented hierarchically for each drug to show:
- The total number of patients with a kidney function check (shown by an eGFR on the record) in the previous 15 months.
- Below is the number of patients found with a kidney function too low using CrCl-CG IBW.
- Below that is the number found if actual weight is used instead of ideal body weight (CrCl-CG AW). Next on that row is the CrCl-CG IBW minus the number found using actual weight which gives the number of patients that would be missed that should have their drug prescription altered.
- Finally is the number found if eGFR is used. Next on that row is CrCl-CG IBW minus the number found using eGFR which gives the number of patients that would be missed that should have their drug prescription altered.

For example, for the 3,436 people aged 65 years and older prescribed alendronic acid:
- 3,436 people taking alendronic acid had a kidney function check (shown by an eGFR on the record) in the previous 15 months. 804 of those were found to have a CrCl-CG IBW below 35ml/min.

drug		aged 65 years and older				aged 85yrs and older			
		total	numbers missed using the other equations rather than CrCl-CG IBW			total	numbers missed using the other equations rather than CrCl-CG IBW		
			number pts missed	% of CrCl-CG IBW	% of total with eGFR		number pts missed	% of CrCl-CG IBW	% of total with eGFR
alendronic acid	eGFR in the last 15 months	3,436				766			
	CrCl-CG IBW < recommended	804				413			
	CrCl-CG AW < recommended	614	190	23.6	5.5	343	70	16.9	9.1
	eGFR < recommended	108	696	86.6	20.3	53	360	87.2	47.0
metformin	eGFR in the last 15 months	6,233				473			
	CrCl-CG IBW < recommended	267				113			
	CrCl-CG AW < recommended	135	132	49.4	2.1	72	41	36.3	6.7
	eGFR < recommended	20	247	92.5	4.0	5	108	95.6	22.8
simvastatin >10mg	eGFR in the last 15 months	19,477				2,063			
	CrCl-CG IBW < recommended	1,465				655			
	CrCl-CG AW < recommended	1,019	446	30.4	2.3	517	138	21.1	6.7
	eGFR < recommended	344	1,121	76.5	5.8	90	565	86.3	27.4
gabapentin or pregabalin	eGFR in the last 15 months	1,233				165			
	CrCl-CG IBW < recommended	132				33			
	CrCl-CG AW < recommended	79	53	40.2	4.3	31	2	6.1	1.2
	eGFR < recommended	41	91	68.9	7.4	11	22	66.7	13.3
nitrofurantoin (acute)	eGFR in the last 15 months	3,226				754			
	CrCl-CG IBW < recommended	1,262				586			
	CrCl-CG AW < recommended	955	307	24.3	9.5	525	61	10.4	8.1
	eGFR < recommended	354	908	71.9	28.1	147	439	74.9	58.2
thiazide	eGFR in the last 15 months	10,876				1,267			
	CrCl-CG IBW < recommended	797				432			
	CrCl-CG AW < recommended	547	250	31.4	2.3	338	94	21.8	7.4
	eGFR < recommended	129	668	83.8	6.1	40	392	90.7	30.9
NSAID	eGFR in the last 15 months	2,498				145			
	CrCl-CG IBW < recommended	86				42			
	CrCl-CG AW < recommended	53	33	38.4	1.3	29	13	31.0	9.0
	eGFR < recommended	4	82	95.3	3.3	2	40	95.2	27.6
ACEI/ARB	eGFR in the last 15 months	26,223				3,215			
	CrCl-CG IBW < recommended	2,521				1,171			
	CrCl-CG AW < recommended	1,687	834	33.1	3.2	896	275	23.5	8.6
	eGFR < recommended	579	1,942	77.0	7.4	160	1,011	86.3	31.4

Abbreviations: ACE: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; CrCl-CG IBW: creatinine clearance Cockcroft Gault using ideal body weight; CrCl-CG AW: creatinine clearance Cockcroft Gault using actual body weight; eGFR: estimated glomerular filtration rate; NSAID: non-steroidal anti-inflammatory.

Table 27: Number of 'patient drug events' where the kidney function was too low, but would be missed if CrCl-CG AW or eGFR are used instead of CrCl-CG IBW.

- Using actual weight in the CrCl-CG calculation would mean that 614 patients would be considered to have too low a kidney function, and 190 patients would have been missed. That is 23.6% of those found using CrCl-CG IBW, and 5.5% of all those taking alendronic acid and with a recent kidney function test.

- Using eGFR would only have found 108 patients with a low kidney function, and 696 of the patients that should have their alendronic acid stopped would be missed; that is 86.6% of those who should have been identified, and 20.3% of all people aged over 65 years prescribed alendronic acid with a recent kidney function test.

Alendronic acid – recommended to be avoided at <35ml/min.

- **Number of patient drug events where a recent kidney function was available but was too low for the recommended use.**

In 3,400 patients aged 65 years and older, 23.6% (CI ±0.04) were prescribed alendronic acid despite a recent kidney function <35 ml/min on the patient record. This was 4.4% (CI ±0.01) of the 1,120 65-74 year olds that had CrCl-CG IBW <35 ml/min, 22.3% (CI ±0.02) of the 1,532 75-84 year olds, and 55.2% (CI ±0.07) of the 748 ≥85 year olds (Table 26).

Number where alendronic acid should be stopped, but would be missed if eGFR were used instead of CrCl-CG using ideal body weight. (Table 27)

For ≥65 year olds, 696 (86.6%) of the cases found with a kidney function too low using CrCl-CG IBW would have been missed if eGFR had been used. That is 20.3% of all the alendronic acid repeat prescriptions studied which had a lower than recommended kidney function but would not be identified if eGFR was used.

For ≥85 year olds, 360 (87.2%) of the cases found with a kidney function too low using CrCl-CG IBW would have been missed if eGFR had been used. That is 47.0% of all the repeat prescriptions studied which had a lower than recommended kidney function but would not be identified if eGFR was used.

Number where alendronic acid should be stopped, but would be missed if actual weight rather than ideal body weight were used in CrCl-CG. (Table 27)

For ≥65 year olds, 190 (23.6%) of the cases found with a kidney function too low using CrCl-CG IBW would have been missed if actual weight had been used. That is 5.5% of all the repeat prescriptions studied which had a lower than recommended kidney function but would not be identified if CrCl-CG AW was used.

For ≥85 year olds, 70 (16.9%) of the cases found with a kidney function too low using CrCl-CG IBW would have been missed if actual weight had been used. That is 9% of all the repeat prescriptions studied which had a lower than recommended kidney function but would not be identified if CrCl-CG AW was used.

- **Line plot charting the range of kidney function at each age level.**

The range of kidney function estimated using CrCl-CG IBW from SrCr, reported within the previous 15 months, for the 3,400 alendronic acid patient drug events are plotted in Figure 16 at each age level from 65 years. The level of 35 ml/min is marked, and any points under the line show use of the drug where the kidney function would be considered too low for recommended use.
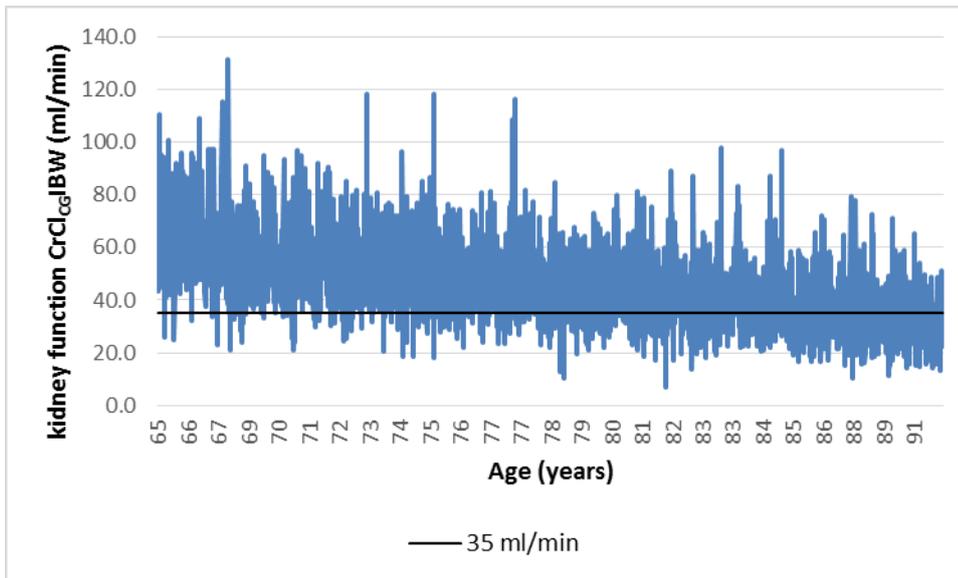
Figure 16: Line plot charting the range of kidney function (CrCl-CG IBW within the previous 15 months) for alendronic acid prescribed for people at each age level 65 years and older.

A Spearman correlation analysis was run to determine the relationship between an individual's age and their level of kidney function. The data showed no violation of linearity. There was a moderate negative correlation between age and level of kidney function, which was statistically significant ($r = -0.579$, $n = 3400$, $p < 0.0005$); kidney function tends to reduce with age in people prescribed alendronic acid.

- **Logistic regression analysis**

Using any of the three equations, compared to age band 65-74yrs, those aged 75-84yrs have higher odds of having a kidney function too low for the alendronic acid prescribed, and those aged 85yrs and over have even higher odds of having a kidney function lower than recommended (Table 28). Using CrCl-CG IBW, patients aged 74-84 years have 6.3 times greater odds of having a kidney function too low to be prescribed alendronic acid, and 26.9 times greater odds for those aged ≥85 years.

		65-74yrs	75-84yrs		85 years and older	
			odds ratio		odds ratio	
	eGFR	1	1.958	(1.076-3.561)	5.486	(3.069-9.807)
alendronic acid	CrCl-CG AW	1	5.107	(3.591-7.264)	24.115	(16.925-34.358)
	CrCl-CG IBW	1	6.282	(4.605-8.569)	26.946	(19.556-37.129)

Abbreviations: CrCl-CG IBW: creatinine clearance Cockcroft Gault using ideal body weight; CrCl-CG AW: creatinine clearance Cockcroft Gault using actual body weight; eGFR: estimated glomerular filtration rate.

Table 28: Odds ratios for the effect of older age on having a kidney function too low to be prescribed alendronic acid.

Metformin – recommended to be avoided at <30ml/min.

- **Number of patient drug events where a recent kidney function was available but was too low for the recommended use.**

In 6,276 patients aged 65 years and older, 4.3% (CI ±0.03) were prescribed metformin despite a recent kidney function <30 ml/min on the patient record, when it is contra-indicated. This was 0.9% (CI ±0.0005) found in the 3,491 65-74 year olds, 5.3% (CI ±0.004) in the 2,319 74-85 year olds, and 24.2% (CI ±0.08) of the 466 ≥85 year olds that had a CrCl-CG IBW <30ml/min (Table 26).

Number where metformin should be stopped, but would be missed if eGFR were used instead of CrCl-CG using ideal body weight. (Table 27)

For ≥65 year olds, 247 (92.5%) of the cases found with a kidney function too low using CrCl-CG IBW would have been missed if eGFR had been used. That is 4.0% of all the repeat prescriptions studied which had a lower than recommended kidney function but would not be identified if eGFR was used.

For ≥85 year olds, 108 (95.6%) of the cases found with a kidney function too low using CrCl-CG IBW would have been missed if eGFR had been used. That is 22.8% of all the repeat prescriptions studied which had a lower than recommended kidney function but would not be identified if eGFR was used.

Number where metformin should be stopped, but would be missed if actual weight rather than ideal body weight were used in CrCl-CG. (Table 27)

For ≥65 year olds, 132 (49.4%) of the cases found with a kidney function too low using CrCl-CG IBW would have been missed if actual weight had been used. That is 2.1% of all the repeat prescriptions studied which had a lower than recommended kidney function but would not be identified if CrCl-CG AW was used.

For ≥85 year olds, 41 (36.3%) of the cases found with a kidney function too low using CrCl-CG IBW would have been missed if actual weight had been used. That is 8.7% of all the repeat prescriptions studied which had a lower than recommended kidney function but would not be picked up if CrCl-CG AW was used.

- **Line plot charting the range of kidney function at each age level.**

The range of kidney function estimated using CrCl-CG IBW from SrCr, reported within the previous 15 months, for the 6,276 metformin patient drug events are plotted in Figure 17 at each age level from 65 years. The level of 30 ml/min is marked, and any points under the line show use of the drug where the kidney function would be considered too low for recommended use. Also marked is the 45 ml/min level, below which caution and reduced dose is recommended.
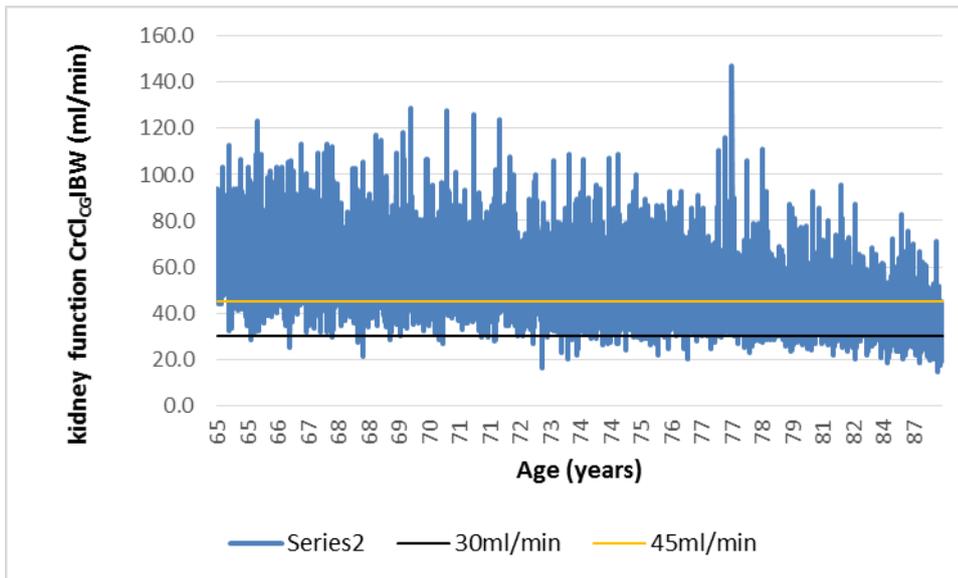
Figure 17: Line plot charting the range of kidney function (CrCl-CG IBW within the previous 15 months) for metformin prescribed for people at each age level 65 years and older.

A Spearman correlation analysis was run to determine the relationship between an individual's age and their level of kidney function. The data showed no violation of linearity. There was a moderate negative correlation between age and level of kidney function, which was statistically significant (r = -0.516, n = 6,276, p < 0.0005); kidney function tends to reduce with age in people prescribed metformin.

- **Logistic regression analysis**

Using CrCl-CG IBW or AW, compared to age band 65-74yrs, those aged 75-84yrs have higher odds of having a kidney function too low for the metformin they were prescribed, and for all 3 equations those aged 85yrs and over have higher odds of having a kidney function lower than recommended (Table 29). Using CrCl-CG IBW patients aged 74-84 years have 6.5 times greater odds of having a kidney function too low to be prescribed metformin, and 36.9 times greater odds for those aged ≥85 years.

		65-74yrs	75-84yrs		85 years and older	
			odds ratio		odds ratio	
	eGFR	1	2.257	(0.802-6.348)	6.145	(1.868-6.348)
metformin	CrCl-CG AW	1	5.896	(3.195-10.877)	48.643	(26.704-88.609)
	CrCl-CG IBW	1	6.517	(4.358-9.746)	36.93	(24.334-58.048)

Abbreviations: CrCl-CG IBW: creatinine clearance Cockcroft Gault using ideal body weight; CrCl-CG AW: creatinine clearance Cockcroft Gault using actual body weight; eGFR: estimated glomerular filtration rate.

Table 29: Odds ratios for the effect of older age on having a kidney function too low to be prescribed metformin.

Simvastatin >10mg – recommended dose reduction at <30 ml/min.

- **Number of patient drug events where a recent kidney function was available but was too low for the recommended use.**

In 19,434 patients aged 65 years and older, simvastatin was prescribed at doses greater than 10mg on repeat prescription for 1,465 (7.5%) (CI ±0.01) despite a recent kidney function <30 ml/min on the patient record. This was 167 (1.7%) (CI ±0.0003) of the 9,894 65-74 year olds that had CrCl-CG IBW <30 ml/min, 643 (8.6%) (CI ±0.002) of the 7,494 75-84 year olds, and 655 (32%) (CI ±0.02) of the 2,046 ≥85 year olds prescribed simvastatin at doses greater than 10mg (Table 26).

Number where simvastatin should be stopped, but would be missed if eGFR were used instead of CrCl-CG using ideal body weight. (Table 27)

For ≥65 year olds, 1,121 (76.5%) of the cases found with a kidney function too low using CrCl-CG IBW would have been missed if eGFR had been used. That is 5.8% of all the repeat prescriptions studied which had a lower than recommended kidney function but would not be identified if eGFR was used.

For ≥85 year olds, 565 (86.3%) of the cases found with a kidney function too low using CrCl-CG IBW would have been missed if eGFR had been used. That is 27.4% of all the repeat prescriptions studied which had a lower than recommended kidney function but would not be picked up if eGFR was used.

Number where metformin should be stopped, but would be missed if actual weight rather than ideal body weight were used in CrCl-CG. (Table 27)

For ≥65 year olds, 446 (30.4%) of the cases found with a kidney function too low using CrCl-CG IBW would have been missed if actual weight had been used. That is 2.3% of all the repeat prescriptions studied which had a lower than recommended kidney function but would not be picked up if CrCl-CG AW was used.

For ≥85 year olds, 138 (21.1%) of the cases found with a kidney function too low using CrCl-CG IBW would have been missed if actual weight had been used. That is 6.7% of all the repeat prescriptions studied which had a lower than recommended kidney function but would not be picked up if CrCl-CG AW was used.

- **Line plot charting the range of kidney function at each age level.**

The range of kidney function estimated using CrCl-CG IBW from SrCr, reported within the previous 15 months, for the 19,434 simvastatin >10mg patient drug events are plotted in Figure 18 at each age level from 65 years. The level of 30 ml/min is marked, and any points under the line show use of the drug where the kidney function would be considered too low for recommended use.
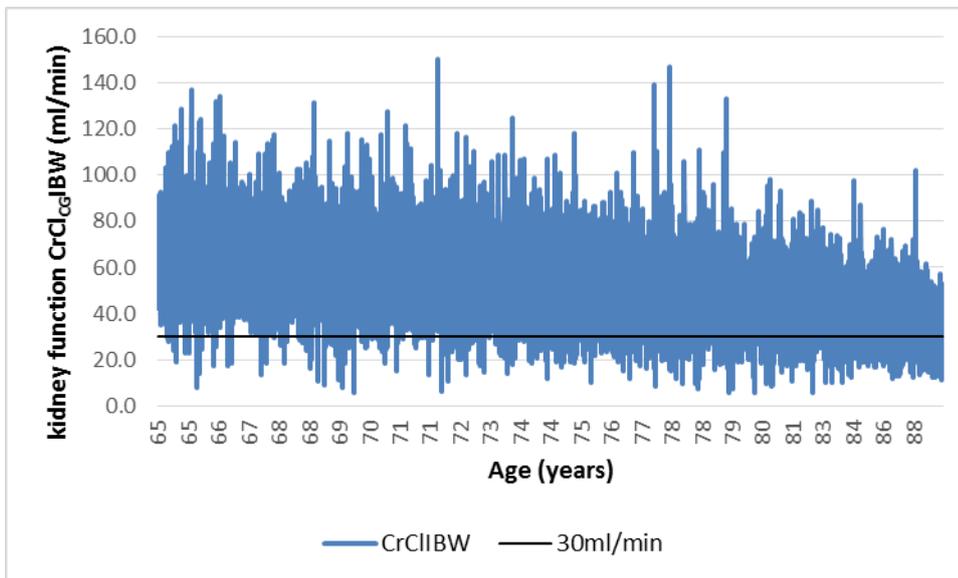
Figure 18: Line plot charting the range of kidney function (CrCl-CG IBW within the previous 15 months) for simvastatin prescribed for people at each age level 65 years and older.

A Spearman correlation analysis was run to determine the relationship between an individual's age and their level of kidney function. The data showed no violation of linearity. There was a moderate negative correlation between age and level of kidney function, which was statistically significant (r = -0.577, n = 19,434, p < 0.0005); kidney function tends to reduce with age in people prescribed simvastatin doses >10mg.

- **Logistic regression analysis**

Using any of the three equations, compared to age band 65-74yrs, those aged 75-84yrs have higher odds of having a kidney function too low for the simvastatin they were prescribed, and those aged 85yrs and over have even higher odds of having a kidney function lower than recommended (Table 30). Using CrCl-CG IBW patients aged 74-84 years have 5.5 times greater odds of having a kidney function too low to be prescribed simvastatin, and 27.4 times greater odds for those aged ≥85 years.

		65-74yrs	75-84yrs		85 years and older	
			odds ratio		odds ratio	
	eGFR	1	2.445	(1.887-3.167)	4.983	(3.706-6.701)
simvastatin >10mg	CrCl-CG AW	1	5.028	(4.055-6.234)	30.635	(24.727-37.95)
	CrCl-CG IBW	1	5.467	(4.598-6.499)	27.427	(22.933-32.802)

Abbreviations: CrCl-CG IBW: creatinine clearance Cockcroft Gault using ideal body weight; CrCl-CG AW: creatinine clearance Cockcroft Gault using actual body weight; eGFR: estimated glomerular filtration rate.

Table 30: Odds ratios for the effect of older age on having a kidney function too low to be prescribed higher dose simvastatin

Gabapentin and pregabalin – recommendations for dose reductions at specified levels of kidney function give in the SPCs.

- **Number of patient drug events where a recent kidney function was available but was too low for the recommended use.**

In 1,209 patients aged 65 years and older, gabapentin or pregabalin were prescribed at doses greater than recommended on repeat prescription for 132 (10.9%) (CI ±0.1) despite a recent kidney function on the patient record being too low for the formulation dose (Table 15). This was 43 (7.2%) (CI ±0.02) of the 598 65-74 year olds, 56 (12.4%) (CI ±0.05) of the 450 75-84 year olds, and 33 (20.5%) (CI ±0.2) of the 161 ≥85 year olds where CrCl-CG IBW was lower than recommended (Table 26).

Number where the dose should be reduced, but would be missed if eGFR were used instead of CrCl-CG using ideal body weight. (Table 27)

For ≥65 year olds, 91 (68.9%) of the cases found with a kidney function too low using CrCl-CG IBW would have been missed if eGFR had been used. That is 7.4% of all the repeat prescriptions studied which had a lower than recommended kidney function but would not be identified if eGFR was used.

For ≥85 year olds, 22 (66.7%) of the cases found with a kidney function too low using CrCl-CG IBW would have been missed if eGFR had been used. That is 13.3% of all the repeat prescriptions studied which had a lower than recommended kidney function but would not be identified if eGFR was used.

Number where the dose of should be reduced, but would be missed if actual weight rather than ideal body weight were used in CrCl-CG. (Table 27)

For ≥65 year olds, 53 (40.2%) of the cases found with a kidney function too low using CrCl-CG IBW would have been missed if actual weight had been used. That is 4.3% of all the repeat prescriptions studied which had a lower than recommended kidney function but would not be identified if CrCl-CG AW was used.

For ≥85 year olds, 2 (6.1%) of the cases found with a kidney function too low using CrCl-CG IBW would have been missed if actual weight had been used. That is 1.2% of all the repeat prescriptions studied which had a lower than recommended kidney function but would not be identified if CrCl-CG AW was used.

- **Line plot charting the range of kidney function at each age level.**

The range of kidney function estimated using CrCl-CG IBW from SrCr, reported within the previous 15 months, for the 1,209 gabapentin and pregabalin patient drug events are plotted in Figure 19 at each age level from 65 years. The levels of 30 ml/min and 60 ml/min are marked.
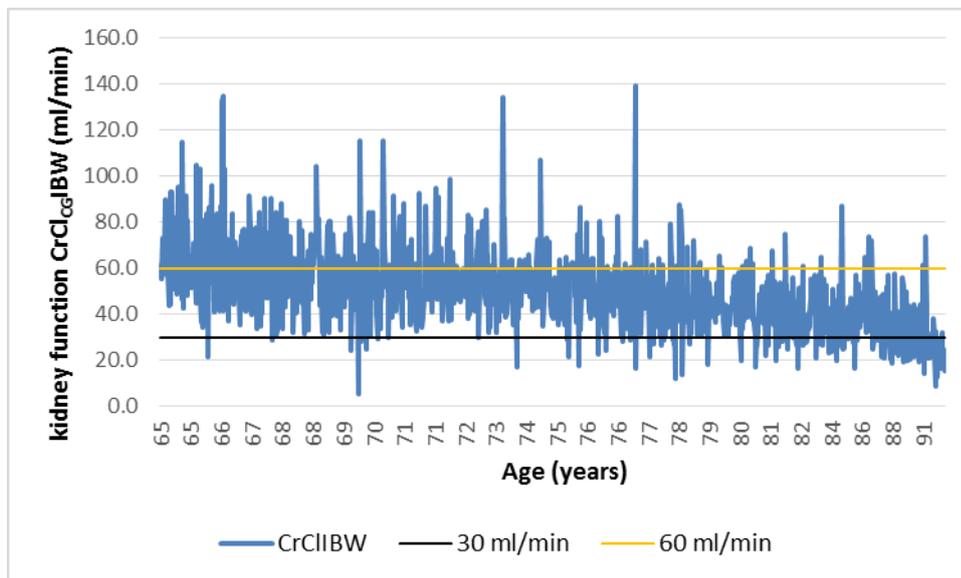
Figure 19: Line plot charting the range of kidney function (CrCl-CG IBW within the previous 15 months) for gabapentin and pregabalin prescribed for people at each age level 65 years and older.

A Spearman correlation analysis was run to determine the relationship between an individual's age and their level of kidney function. The data showed no violation of linearity. There was a moderate negative correlation between age and level of kidney function, which was statistically significant (r = -0.565, n = 1,209 p < 0.0005); kidney function tends to reduce with age in people prescribed gabapentin and pregabalin.

- **Logistic regression analysis**

Using any of the three equations, compared to age band 65-74yrs, those aged 75-84yrs have higher odds of having a kidney function too low for the gabapentin or pregabalin they were prescribed, and those aged 85yrs and over have even higher odds of having a kidney function lower than recommended (Table 31). Using CrCl-CG IBW patients aged 74-84 years have 1.8 times greater odds of having a kidney function too low to be prescribed gabapentin or pregabalin, and 3.3 times greater odds for those aged 85 years and older.

		65-74yrs	75-84yrs		85 years and older	
			odds ratio		odds ratio	
	eGFR	1	2.729	(1.265-5.888)	4.279	(1.784-10.258)
Gabapentin/pregabalin	CrCl-CG AW	1	2.972	(1.545-5.717)	9.958	(5.251-18.884)
	CrCl-CG IBW	1	1.834	(1.208-2.786)	3.328	(2.033-5.446)

Abbreviations: CrCl-CG IBW: creatinine clearance Cockcroft Gault using ideal body weight; CrCl-CG AW: creatinine clearance Cockcroft Gault using actual body weight; eGFR: estimated glomerular filtration rate.

Table 31: Odds ratios for the effect of older age on having a kidney function too low to be prescribed too high a dose of gabapentin or pregabalin.

Nitrofurantoin – ineffective below 45 ml/min

- **Number of patient drug events where a recent kidney function was available but was too low for the recommended use.**

In 3,185 patients aged 65 years and older prescribed nitrofurantoin in the previous 12 months, 1,262 (39.6%) (CI ±0.04) were prescribed despite a recent kidney function <45 ml/min on the patient record. This was 141 (11.7%) (CI ±0.02) of the 1,206 aged 65-74 years, 535 (43.1%) (CI ±0.04) of the 1,252 75-84 year olds, and 586 (79.5%) (CI ± 0.04) of the 85 years and older patients with a recent CrCl-CG IBW <45 ml/min (Table 26).

Number where nitrofurantoin would be ineffective, but would be missed if eGFR were used instead of CrCl-CG using ideal body weight. (Table 27)

For ≥65 year olds, 908 (71.9%) of the cases found with a kidney function too low using CrCl-CG IBW would have been missed if eGFR had been used. That is 28.1% of all the repeat prescriptions studied which had a lower than recommended kidney function but would not be identified if eGFR was used.

For ≥85 year olds, 439 (74.9%) of the cases found with a kidney function too low using CrCl-CG IBW would have been missed if eGFR had been used. That is 58.2% of all the repeat prescriptions studied which had a lower than recommended kidney function but would not be identified if eGFR was used.

Number where nitrofurantoin would be ineffective, but would be missed if actual weight rather than ideal body weight were used in CrCl-CG. (Table 27)

For ≥65 year olds, 307 (24.3%) of the cases found with a kidney function too low using CrCl-CG IBW would have been missed if actual weight had been used. That is 9.5% of all the repeat prescriptions studied which had a lower than recommended kidney function but would not be identified if CrCl-CG AW was used.

For ≥85 year olds, 61 (10.4%) of the cases found with a kidney function too low using CrCl-CG IBW would have been missed if actual weight had been used. That is 8.1% of all the repeat prescriptions studied which had a lower than recommended kidney function but would not be identified if CrCl-CG AW was used.

- **Line plot charting the range of kidney function at each age level.**

The range of kidney function estimated using CrCl-CG IBW from SrCr, reported within the previous 15 months, for the 3,185 nitrofurantoin patient drug events are plotted in Figure 20 at each age level from 65 years. The level of 45 ml/min is marked, and any points under the line show use of the drug where the kidney function would be considered too low to be effective.
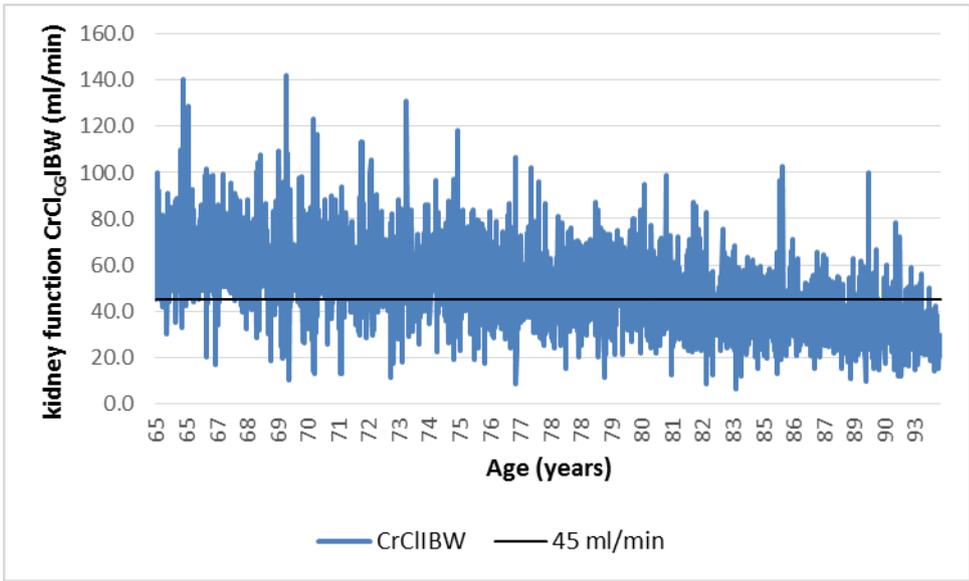
Figure 20: Line plot charting the range of kidney function (CrCl-CG IBW within the previous 15 months) for nitrofurantoin prescribed for people at each age level 65 years and older.

A Spearman correlation analysis was run to determine the relationship between an individual's age and their level of kidney function. The data showed no violation of linearity. There was a moderate negative correlation between age and level of kidney function, which was statistically significant (r = -0.608, n = 3,185 p < 0.0005); kidney function tends to reduce with age in people prescribed nitrofurantoin.

- **Logistic regression analysis**

Using any of the three equations, compared to age band 65-74yrs, those aged 75-84yrs have higher odds of having a kidney function too low for the nitrofurantoin they were prescribed, and those aged 85yrs and over have even higher odds of having a kidney function lower than recommended (Table 32). Using CrCl-CG IBW patients aged 74-84 years have 5.6 times greater odds of having a kidney function too low to be prescribed nitrofurantoin, and 29.2 times greater odds for those aged 85 years and older.

		65-74yrs	75-84yrs		85 years and older	
			odds ratio		odds ratio	
nitrofurantoin	eGFR	1	3.03	(4.198-4.177)	5.243	(3.781-7.27)
	CrCl-CG AW	1	6.786	(5.161-8.923)	41.334	(30.865-55.356)
	CrCl-CG IBW	1	5.644	(4.581-6.952)	29.23	(22.748-37.559)

Abbreviations: CrCl-CG IBW: creatinine clearance Cockcroft Gault using ideal body weight; CrCl-CG AW: creatinine clearance Cockcroft Gault using actual body weight; eGFR: estimated glomerular filtration rate.

Table 32: Odds ratios for the effect of older age on having a kidney function too low to for nitrofurantoin to be effective.

Thiazides – ineffective below 30 ml/min

- **Number of patient drug events where a recent kidney function was available but was too low for the recommended use.**

In 10,805 patients aged 65 years and older prescribed thiazides on repeat prescription, 797 (7.4%) (CI ±0.02) were prescribed despite a recent kidney function <30 ml/min on the patient record. This was 62 (1.2%) (CI ±0.0004) of the 5,371 65-74 year olds, 303 (7.2%) (CI ±0.003) of the 4,189 75-84 year olds, and 432 (34.7%) (CI ±0.04) of the ≥85 year olds with a CrCl-CG IBW <30 ml/min (Table 26).

Number where a thiazide would be ineffective, but would be missed if eGFR were used instead of CrCl-CG using ideal body weight. (Table 27)

For ≥65 year olds, 668 (83.8%) of the cases found with a kidney function too low using CrCl-CG IBW would have been missed if eGFR had been used. That is 6.1% of all the repeat prescriptions studied which had a lower than recommended kidney function but would not be identified if eGFR was used.

For ≥85 year olds, 392 (90.7%) of the cases found with a kidney function too low using CrCl-CG IBW would have been missed if eGFR had been used. That is 30.9% of all the repeat prescriptions studied which had a lower than recommended kidney function but would not be identified if eGFR was used.

Number where a thiazide would be ineffective, but would be missed if actual weight rather than ideal body weight were used in CrCl-CG. (Table 27)

For ≥65 year olds, 250 (31.4%) of the cases found with a kidney function too low using CrCl-CG IBW would have been missed if actual weight had been used. That is 2.3% of all the repeat prescriptions studied which had a lower than recommended kidney function but would not be identified if CrCl-CG AW was used.

For ≥85 year olds, 94 (21.8%) of the cases found with a kidney function too low using CrCl-CG IBW would have been missed if actual weight had been used. That is 7.4% of all the repeat prescriptions studied which had a lower than recommended kidney function but would not be identified if CrCl-CG AW was used.

- **Line plot charting the range of kidney function at each age level.**

The range of kidney function estimated using CrCl-CG IBW from SrCr, reported within the previous 15 months, for the 10,805 thiazide patient drug events are plotted in Figure 21 at each age level from 65 years. The level of 30 ml/min is marked, and any points under the line show use of the drug where the kidney function would be considered too low to be effective.
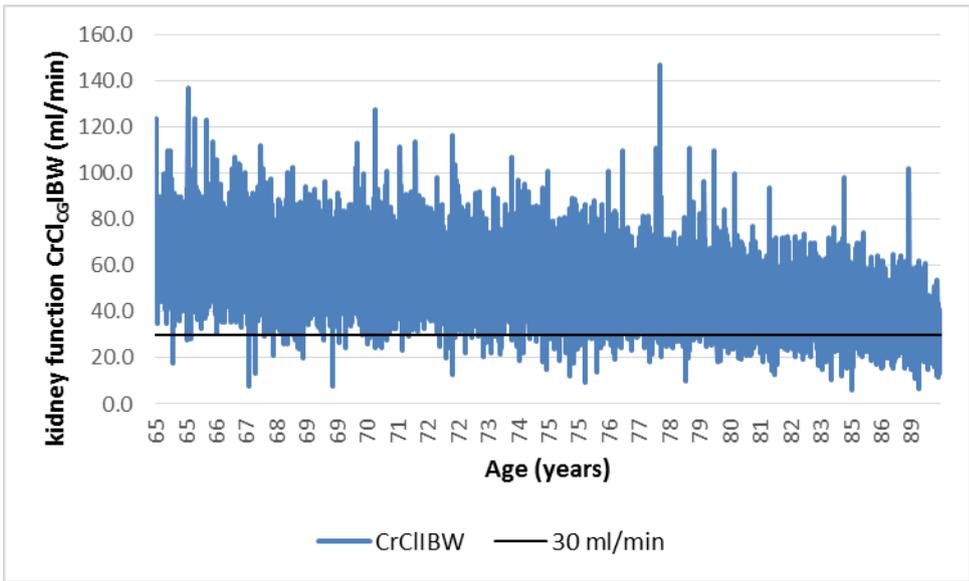
Figure 21: Line plot charting the range of kidney function (CrCl-CG IBW within the previous 15 months) for thiazides prescribed for people at each age level 65 years and older.

A Spearman correlation analysis was run to determine the relationship between an individual's age and their level of kidney function. The data showed no violation of linearity. There was a moderate negative correlation between age and level of kidney function, which was statistically significant (r = -0.573, n = 10,805 p < 0.0005); kidney function tends to reduce with age in people prescribed a thiazide.

- **Logistic regression analysis**

Using any of the three equations, compared to age band 65-74yrs, those aged 75-84yrs have higher odds of having a kidney function too low for the thiazide they were prescribed, and those aged 85yrs and over have even higher odds of having a kidney function lower than recommended (Table 33). Using CrCl-CG IBW patients aged 74-84 years have 6.7 times greater odds of having a kidney function too low to be prescribed a thiazide, and 45.5 times greater odds for those aged 85 years and older.

		65-74yrs	75-84yrs		85 years and older	
			odds ratio		odds ratio	
	eGFR	1	2.185	(1.418-3.365)	5.293	(3.324-8.427)
thiazides	CrCl-CG AW	1	5.603	(3.960-7.927)	49.666	(35.521-69.444)
	CrCl-CG IBW	1	6.677	(5.065-8.802)	45.5	(34.518-59.976)

Abbreviations: CrCl-CG IBW: creatinine clearance Cockcroft Gault using ideal body weight; CrCl-CG AW: creatinine clearance Cockcroft Gault using actual body weight; eGFR: estimated glomerular filtration rate.

Table 33: Odds ratios for the effect of older age on having a kidney function too low for a thiazide to be effective.

NSAIDs – caution in RKF as frequently cause ADRs

- **Number of patient drug events where a recent kidney function was available but was too low for the recommended use.**

In 2,483 patients aged 65 years and older prescribed NSAIDS on repeat prescription, 86 (3.5%) (CI ±0.08) were prescribed despite a recent kidney function <30 ml/min on the patient record. This was 8 (0.5%) (CI ±0.001) of 1,577 65-74 year olds, 36 (4.7%) (CI ±0.01) of the 762 75-84 years, and 42 (29.2%) (CI ±0.3) of the 144 patients aged 85 years and older with a CrCl-CG IBW <30 ml/min (Table 26).

Number where an NSAID should be stopped, but would be missed if eGFR were used instead of CrCl-CG using ideal body weight. (Table 27)

For ≥65 year olds, 82 (95.3%) of the cases found with a kidney function too low using CrCl-CG IBW would have been missed if eGFR had been used. That is 3.3% of all the repeat prescriptions studied which had a lower than recommended kidney function but would not be identified if eGFR was used.

For ≥85 year olds, 40 (95.2%) of the cases found with a kidney function too low using CrCl-CG IBW would have been missed if eGFR had been used. That is 27.6% of all the repeat prescriptions studied which had a lower than recommended kidney function but would not be identified if eGFR was used.

Number where an NSAID should be stopped, but would be missed if actual weight rather than ideal body weight were used in CrCl-CG. (Table 27)

For ≥65 year olds, 33 (38.4%) of the cases found with a kidney function too low using CrCl-CG IBW would have been missed if actual weight had been used. That is 1.3% of all the repeat prescriptions studied which had a lower than recommended kidney function but would not be picked up if CrCl-CG AW was used.

For ≥85 year olds, 13 (31.0%) of the cases found with a kidney function too low using CrCl-CG IBW would have been missed if actual weight had been used. That is 9.0% of all the repeat prescriptions studied which had a lower than recommended kidney function but would not be identified if CrCl-CG AW was used.

- **Line plot charting the range of kidney function at each age level.**

The range of kidney function estimated using CrCl-CG IBW from SrCr, reported within the previous 15 months, for the 2,483 NSAID patient drug events are plotted in Figure 22 at each age level from 65 years. The level of 30 ml/min is marked, as the level used in the analysis. The 60 ml/min level is also shown on the graph as use of NSAIDs in any degree of reduced kidney function needs caution and assessment.
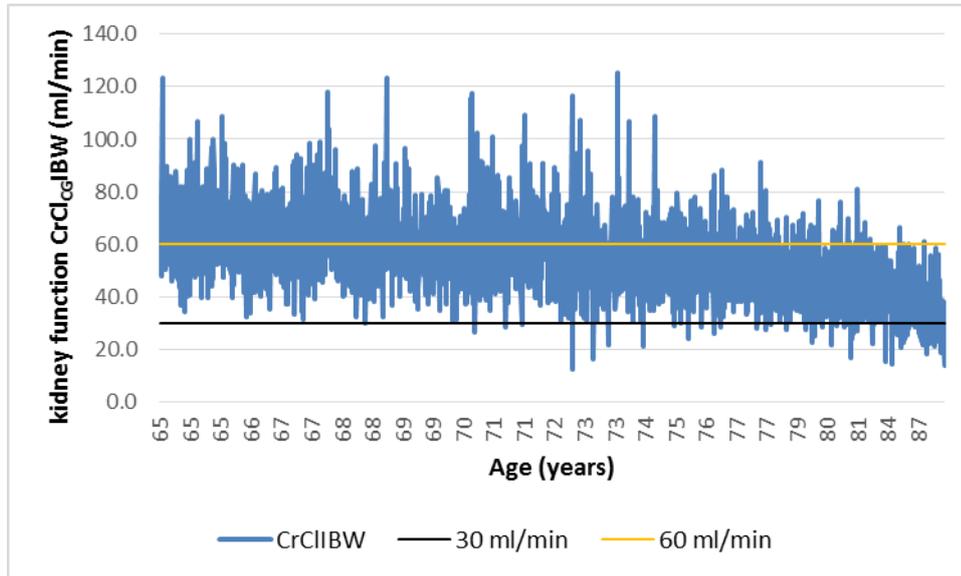
Figure 22: Line plot charting the range of kidney function (CrCl-CG IBW within the previous 15 months) for NSAIDs prescribed for people at each age level 65 years and older.

A Spearman correlation analysis was run to determine the relationship between an individual's age and their level of kidney function. The data showed no violation of linearity. There was a moderate negative correlation between age and level of kidney function, which was statistically significant ($r = -0.497$, $n = 2,483$ $p < 0.0005$); kidney function tends to reduce with age in people prescribed an NSAID.

- **Logistic regression analysis**

Using any of the three equations, compared to age band 65-74yrs, those aged 75-84yrs have higher odds of having a kidney function too low for the NSAID they were prescribed, and those aged 85yrs and over have even higher odds of having a kidney function lower than recommended (Table 34). Using CrCl-CG IBW patients aged 74-84 years have 9.7 times greater odds of having a kidney function too low to be prescribed an NSAID, and 80.8 times greater odds for those aged 85 years and older.

		65-74yrs	75-84yrs		85 years and older	
			odds ratio		odds ratio	
	eGFR	1	4.201	(1.048-16.843)	3.676	(0.380-35.566)
NSAIDs	CrCl-CG AW	1	3.498	(1.524-8.031)	43.934	(20.313-95.026)
	CrCl-CG IBW	1	9.725	(4.498-21.028)	80.757	(36.94-176.549)

Abbreviations: CrCl-CG IBW: creatinine clearance Cockcroft Gault using ideal body weight; CrCl-CG AW: creatinine clearance Cockcroft Gault using actual body weight; eGFR: estimated glomerular filtration rate.

Table 34: Odds ratios for the effect of older age on having a kidney function too low to be prescribed and NSAID.

ACEIs and ARBs – although used in CKD, they can have an adverse effect on the kidneys and need caution in low levels of kidney function.

- **Number of patient drug events where a recent kidney function was available but was too low for the recommended use.**

In 26,109 patients aged 65 years and older prescribed ACEIs or ARBs on repeat prescription, 2,521 (9.7%) (CI ±0.01) were prescribed where there was a recent kidney function <30 ml/min on the patient record. This was 288 (2.3%) (CI ±0.0004) of 12,663 65-74 year olds, 1,062 (10.3%) (CI ±0.002) of 10,280 75-84 year olds, and 1,171 (37%) (CI ±0.01) of 3,166 patients aged 85 years and older with a recent CrCl-CG IBW <30 ml/min (Table 26).

Number where an ACEI/ARB should be stopped or dose reduced, but would be missed if eGFR were used instead of CrCl-CG using ideal body weight. (Table 27)
For ≥65 year olds, 1,942 (77.0%) of the cases found with a kidney function too low using CrCl-CG IBW would have been missed if eGFR had been used. That is 7.4% of all the repeat prescriptions studied which had a lower than recommended kidney function but would not be identified if eGFR was used.

For ≥85 year olds, 1,011 (86.3%) of the cases found with a kidney function too low using CrCl-CG IBW would have been missed if eGFR had been used. That is 31.4% of all the repeat prescriptions studied which had a lower than recommended kidney function but would not be identified if eGFR was used.

Number where an ACEI/ARB should be stopped or dose reduced, but would be missed if actual weight were used in CrCl-CG. (Table 27)
For ≥65 year olds, 834 (33.1%) of the cases found with a kidney function too low using CrCl-CG IBW would have been missed if actual weight had been used. That is 3.2% of all the repeat prescriptions studied which had a lower than recommended kidney function but would not be identified if CrCl-CG AW was used.

For ≥85 year olds, 275 (23.5%) of the cases found with a kidney function too low using CrCl-CG IBW would have been missed if actual weight had been used. That is 8.6% of all the repeat prescriptions studied which had a lower than recommended kidney function but would not be identified if CrCl-CG AW was used.

- **Line plot charting the range of kidney function at each age level.**

The range of kidney function estimated using CrCl-CG IBW from SrCr, reported within the previous 15 months, for the 26,109 patient ACEI and ARB drug events are plotted in Figure 23 at each age level from 65 years. The level of 30 ml/min is marked, and any points under the line show where caution and reassessment may be required.
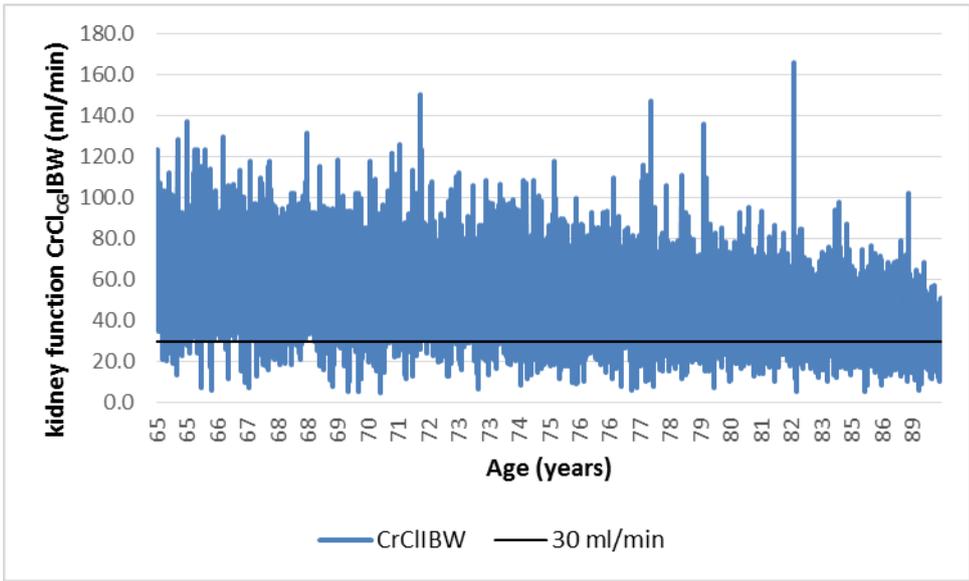
Figure 23: Line plot charting the range of kidney function (CrCl-CG IBW within the previous 15 months) for ACEI/ARBs at each age level 65 years and older.

A Spearman correlation analysis was run to determine the relationship between an individual's age and their level of kidney function. The data showed no violation of linearity. There was a moderate negative correlation between age and level of kidney function, which was statistically significant (r = -0.585, n = 26,109 p < 0.0005); kidney function tends to reduce with age in people prescribed an ACEI or ARB.

- **Logistic regression analysis**

Using any of the three equations, compared to age band 65-74yrs, those aged 75-84yrs have higher odds of having a kidney function too low for the ACE or ARB they were prescribed, and those aged 85yrs and over have even higher odds of having a kidney function lower than recommended (Table 35). Using CrCl-CG IBW patients aged 74-84 years have 5.0 times greater odds of having a kidney function too low to be prescribed an ACEI or ARB, and 25.2 times greater odds for those aged 85 years and older.

		65-74yrs	75-84yrs		85 years and older	
			odds ratio		odds ratio	
ACE/ARBs	eGFR	1	1.811	(1.488-2.205)	3.842	(3.086-4.784)
	CrCl-CG AW	1	4.725	(3.979-5.610)	29.007	(24.273-34.38)
	CrCl-CG IBW	1	4.95	(4.334-5.654)	25.221	(21.985-28.933)

Abbreviations: CrCl-CG IBW: creatinine clearance Cockcroft Gault using ideal body weight; CrCl-CG AW: creatinine clearance Cockcroft Gault using actual body weight; eGFR: estimated glomerular filtration rate.

Table 35: Odds ratios for the effect of older age on having a kidney function too low to be prescribed an ACEI or ARB, or for the dose.

			aged 65-74yrs	aged 75-84yrs	aged 85yrs and older
on alendronic acid		total on drug	1,471	1,827	932
	eGFR	number with an eGFR in the last 15 months	1,122	1,548	766
		number with eGFR < recommended	15	40	53
		% < recommended of those with an eGFR	1.3	2.6	6.9
	CrCl AW	total with a CrCl AW in the last 15 months	1,120	1,532	748
(avoid if <35ml/min)		number with CrCl AW < recommended	38	233	343
		% < recommended of those with a CrCl AW	3.4	15.2	45.9
	CrCl IBW	total with a CrCl IBW in the last 15 months	1,120	1,532	748
		number with CrCl IBW < recommended	49	342	413
		% < recommended of those with a CrCl IBW	4.4	22.3	55.2
on metformin		total on drug	3,594	2,365	480
	eGFR	number with an eGFR in the last 15 months	3,457	2,303	473
		number with eGFR < recommended	6	9	5
		% < recommended of those with an eGFR	0.2	0.4	1.1
	CrCl AW	total with a CrCl AW in the last 15 months	3,491.0	2,319.0	468
(avoid if <30ml/min)		number with CrCl AW < recommended	13	50	72
		% < recommended of those with a CrCl AW	0.4	2.2	15.4
	CrCl IBW	total with a CrCl IBW in the last 15 months	3,491	2,319	466
		number with CrCl IBW < recommended	30	124	113
		% < recommended of those with a CrCl IBW	0.9	5.3	24.2
on simvastatin > 10mg		total on drug	11,200	8,249	2,284
	eGFR	number with an eGFR in the last 15 months	9,922	7,492	2,063
		number with eGFR < recommended	90	164	90
		% < recommended of those with an eGFR	0.9	2.2	4.4
	CrCl AW	total with a CrCl AW in the last 15 months	9,893	7,494	2,046
(max dose 10mg id <30ml/min)		number with CrCl AW < recommended	108	394	517
		% < recommended of those with a CrCl AW	1.1	5.3	25.3
	CrCl IBW	total with a CrCl IBW in the last 15 months	9,894	7,494	2,046
		number with CrCl IBW < recommended	167	643	655
		% < recommended of those with a CrCl IBW	1.7	8.6	32.0
on gabapentin or pregabalin		total on drug	725	526	197
	eGFR	number with an eGFR in the last 15 months	609	459	165
		number with eGFR < recommended	10	20	11
		% < recommended of those with an eGFR	1.6	4.4	6.7
(reduce dose or avoid - see SmPC tables)	CrCl AW	total with a CrCl AW in the last 15 months	598	421	161
		number with CrCl AW < recommended	14	28	31
		% < recommended of those with a CrCl AW	2.3%	6.7%	19.3%
	CrCl IBW	total with a CrCl IBW in the last 15 months	598	450	161
		number with CrCl IBW < recommended	43	56	33
		% < recommended of those with a CrCl IBW	7.2	12.4	20.5

nitrofurantoin (acute) in the prvious 12 months (ineffective <45ml/min)		total on drug	1,356	1,322	811
	eGFR	number with an eGFR in the last 15 months	1,226	1,246	754
		number with eGFR < recommended	54	153	147
		% < recommended of those with an eGFR	4.4	12.3	19.5
	CrCl AW	total with a CrCl AW in the last 15 months	1,206	1,242	737
		number with CrCl AW < recommended	68	362	525
		% < recommended of those with a CrCl AW	5.6	29.1	71.2
	CrCl IBW	total with a CrCl IBW in the last 15 months	1,206	1,242	737
		number with CrCl IBW < recommended	141	535	586
		% < recommended of those with a CrCl IBW	11.7	43.1	79.5
on a thiazide (ineffiective if <30ml/min)		total on drug	5,993	4,662	1443
	eGFR	number with an eGFR in the last 15 months	5,391	4,218	1,267
		number with eGFR < recommended	33	56	40
		% < recommended of those with an eGFR	0.6	1.3	3.2
	CrCl AW	total with a CrCl AW in the last 15 months	5,371	4,189	1,245
		number with CrCl AW < recommended	40	169	338
		% < recommended of those with a CrCl AW	0.7	4.0	27.1
	CrCl IBW	total with a CrCl IBW in the last 15 months	5,371	4,189	1,245
		number with CrCl IBW < recommended	62	303	432
		% < recommended of those with a CrCl IBW	1.2	7.2	34.7
on an NSAID (caution/avoid <30ml/min)		total on drug	2,194	987	182
	eGFR	number with an eGFR in the last 15 months	1,591	762	145
		number with eGFR < recommended	1	1	2
		% < recommended of those with an eGFR	0.1	0.1	1.4
	CrCl AW	total with a CrCl AW in the last 15 months	1,577	762	144
		number with CrCl AW < recommended	9	15	29
		% < recommended of those with a CrCl AW	0.6	2.0	20.1
	CrCl IBW	total with a CrCl IBW in the last 15 months	1,577	762	144
		number with CrCl IBW < recommended	8	36	42
		% < recommended of those with a CrCl IBW	0.5	4.7	29.2
on ACE/ARB (caution/reduce dose <30ml/min)		total on drug	13,739	11,023	3,490
	eGFR	number with an eGFR in the last 15 months	12,716	10,292	3,215
		number with eGFR < recommended	171	248	160
		% < recommended of those with an eGFR	1.3	2.4	5.0
	CrCl AW	total with a CrCl AW in the last 15 months	12,663	10,280	3,166
		number with CrCl AW < recommended	170	621	896
		% < recommended of those with a CrCl AW	1.3	6.0	28.3
	CrCl IBW	total with a CrCl IBW in the last 15 months	12,663	10,280	3,166
		number with CrCl IBW < recommended	288	1062	1171
		% < recommended of those with a CrCl IBW	2.3	10.3	37.0

Abbreviations: ACE: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; CrCl-CG IBW: creatinine clearance Cockcroft Gault using ideal body weight; CrCl-CG AW: creatinine clearance Cockcroft Gault using actual body weight; eGFR: estimated glomerular filtration rate; NSAID: non-steroidal anti-inflammatory.

Table 36: Number of patient drug events where kidney function was found to be below recommended, using eGFR, CrCl-CG AW or CrCl-CG IBW.

3.5.6 Patients found with a kidney function too low using eGFR and CrCl-CG IBW

Figure **24** presents the percentage of 'patient drug events' found where kidney function was assessed to be too low using eGFR (top) and the percentage of 'patient drug events' found where kidney function was assessed to be too low using CrCl-CG IBW (bottom). The figures are taken from the full table of results (Table 36).
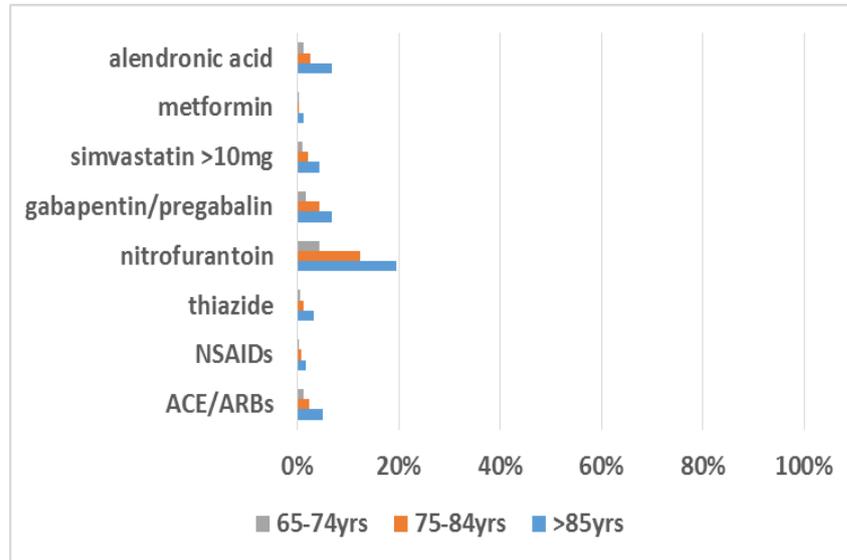
% on each drug identified with RKF using eGFR
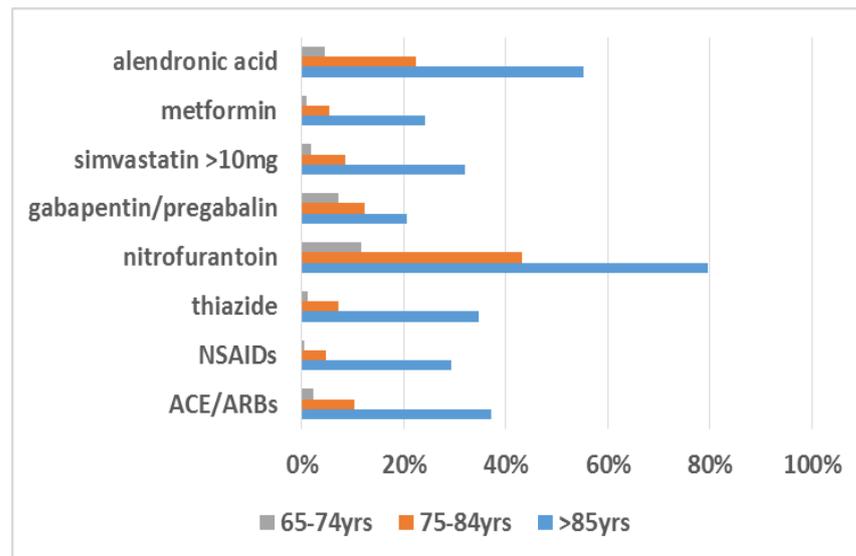
% on each drug identified with RKF using CrCl-CG IBW

Figure 24: A comparison between the percentage of patient drug events where kidney function was too low by eGFR (top) and CrCl-CG IBW (bottom) in the 3 age bands (from Table 36).

3.6 Discussion

3.6.1 Data quality

The study population numbers (Table 22) were comparable to the Office of National Statistics 2011 figures for Bradford (Table 18) suggesting this was a representative population in the former Bradford & Airedale PCT area. The Bradford population has a lower proportion of older people than the national average which could mean that any findings in this study relating to people aged 65 years and older might be an underestimate for the wider UK population.

As a large PCT, Bradford & Airedale had a broad range of prescribers, from medical students to GP trainers, and GP practices ranging from single-handed GPs to large group teaching practices, making it likely that they are representative of GPs nationally.

3.6.2 Missing data analysis

A missing data analysis was completed to ensure that any missing variables were identified, the effect on the final analyses assessed, and to flag up any potential for bias. Virtually no ages or genders were not available, which is as expected as the GP patient record systems have age and gender as required fields.

The data taken from the prescribing database was only from patients who had kidney function test figures on their record which means that those variables would be likely to be complete. Numbers of patients who do not have an eGFR on their record were also searched on the database, and the number of patients without the variables needed to calculate creatinine clearance were calculated from the data. However, very few patients prescribed the study drugs did not have any kidney function on the record.

As only a small number of data need to be excluded, or was not available, there is a greater confidence in the findings being representative of the whole Bradford PCT older population.

3.6.3 Principal findings

3.6.3.1 Prevalence of inappropriate prescribing in RKF

This is the first prevalence study of inappropriate prescribing of drugs affected by reduced kidney function for older people in UK primary care. For all the sampled drugs, and for all age bands, prescribing was found where the kidney function (as measured by CrCl-CG IBW) was too low for recommended use, and particularly for those aged 85 years and older.

The degree of inappropriate drug use and dosing varied from 13.3% to 79% in the prevalence studies found in the scoping literature review (Section 2.5), showing a high degree of inappropriate prescribing, and of the recommendations for use in RKF not being followed in the 14 different countries from which the studies were reported (Table 9). Khanal et al (2015) in Australia also used CrCl-CG as the kidney function estimate and found 28.1 % of patients aged 65 years and older had evidence of inappropriate prescribing of at least one of the 31 renally cleared drugs examined in their study,. The Breton et al study in French primary care (2011) used MDRD and so was likely to find a smaller proportion; even so, they found 13.3% exposure to the risk of inappropriate prescribing for people aged 65 years and older. They also looked at prevalence for lower kidney function finding 52.5% were on inappropriate drugs or doses in those with an eGFR of 30–59, and 96% in those <30ml/min/1.73m^2. A retrospective case record analysis from patients aged over 70 years in a Hull hospital showed a similar level of inappropriate prescribing of renally excreted drugs to this study. They found of 81 out of the 622 medications prescribed (13%) were 'inappropriate' (Jones and Bhandari, 2013).

The current study found that kidney function levels varied widely at all ages studied, showing that kidney function does need to be checked, and drug use assessed, when prescribing these drugs for older people. It has also been shown that kidney function tends to reduce with increasing age for all the eight drugs, and will need assessment of kidney function in relation to the drug choice and dose.

3.6.3.2 Many older people are taking drugs affected by kidney function

The numbers of older people found taking the study drugs were large, with 39.9% of all people aged ≥65 years prescribed an ACEI or ARB, meaning that the impact of prescribing drugs that have recommendations in RKF, for older people is high if kidney function is low. The only comparison found reported in the literature is the French

primary care study (Breton et al, 2011) which found 17.1% were on ACEI/ARBs, 15.5% on a statin, 2.4% metformin, 2.8% bisphosphonates, 8.7% NSAIDs. A larger number of the Bradford & Airedale whole PCT population of 70,900 people aged 65 years and older in 2011 were on the sampled drugs, except for NSAIDs (and it could not be deciphered the numbers for nitrofurantoin or gabapentin/pregabalin).

Non-steroidal anti-inflammatory drugs (NSAIDs) were on the repeat medication list for 3,363 people (4.7%); this may be an underestimate of the total use of NSAIDs in this population as there had been initiatives to reduce regular use and many more are prescribed as an 'acute', when needed basis. Also, 'low dose aspirin' was not included in the searches for NSAIDS; they are classified in a different section on the prescribing database and in the BNF, but although 'low dose', aspirin is an NSAID and can cause all the adverse effects of the higher dose drugs. The numbers would have been very much higher for NSAIDs if low dose aspirin had been included as it is used widely to reduce risk for cardiovascular disease patients.

Use of all the sampled drugs is similar in the over 85 year olds. Use of alendronic acid is higher which reflects increased incidence, and risk, of osteoporosis at increased age, and nitrofurantoin use is also higher which may be due to more urinary tract infections in older females. Use is only slightly lower for the cardiovascular drugs ACEI/ARBs, simvastatin and thiazides.

Petty et al (2014) have reported that the mean total number of medicines per patient on repeat prescriptions is over 5 for the 60-69 year olds, and up to 7.1 for the over 80s so there is the probability that many people will be taking more than one drug eliminated via the kidneys, increasing the complexity of the impact.

3.6.3.3 Age is a factor in having a kidney function estimate too low for recommended use of the study drugs.

The Spearman's correlation analyses showed a moderate negative correlation for age and kidney function level for all the sampled drugs. There was a trend to decreased kidney function level with increased age. This finding fits with the evidence that shows there is a progressive loss of kidney function with aging (Beers and Berkow, 2000; Grimley-Evans et al, 2000; Glassock and Winearis, 2009). All the prevalence data for inappropriate prescribing of each of the 8 drugs for people aged 85 years and older were higher than the younger age groups.

The logistic regression analysis showed that, compared to patients aged 65-74yrs, those aged 75-84yrs have higher odds of having a kidney function too low for the drug they are taking, and those aged 85yrs and over have even higher odds. Age has been shown to

predict higher odds of having a kidney function estimate too low for recommended use of the investigation drug. However, this analysis does not address the possibility of confounding, where a non-casual association is observed between a given exposure and outcome is as a result of the influence of a third variable (Szumilas, 2010). The findings need to be interpreted with this in mind, where there may be a factor not considered affecting the results. Stratification and multiple regression techniques are two methods used to address confounding, and produce 'adjusted' odds ratios, but were not within the scope of this analysis. However, there is broad evidence that kidney function reduces with age and therefore it is likely that, if prescribers are not assessing kidney function in relation to drugs, then this will have a greater impact for older people.

The eGFR has been shown to overestimate kidney function for older people and so is less likely to show differences. However, even using eGFR, a higher odds of having a kidney function too low for the drug being taken was shown for both older age groups and all drugs except for metformin in the 75-84 years age band and the NSAIDs ≥85 years age band (the low numbers in this group might have been a factor).

Khanal et al (2014), in Australia, did a multivariate logistic regression on their data and the factors independently associated with patients being prescribed one or more potentially inappropriate renally cleared drugs were advancing age, the total number of renally cleared drugs prescribed, presence of diabetes, presence of heart failure and living in aged care facilities.

3.6.3.4 Kidney function is tested for most older people

A kidney function estimate was found to be available on the patient record for most of the patients taking the study drugs, and only 2.8%-17.5% did not have a test within the previous 15 months, meaning that kidney function could have been assessed to determine appropriateness of prescribing. This contrasts with many studies found in the scoping review where a kidney function record was not available, for example Corsonello et al (2, 2005) where 32% had to be excluded because there was no documented information on their kidney function.

The UK Quality Outcomes Framework (QOF) targets may have helped as kidney function testing has been incentivised in, for example, diabetes, so with 40% being on an ACEI/ARB they are all likely to have kidney function testing (Quality Outcomes Framework, 2015). However, despite the large proportion of the patients having a recent kidney function estimate on their record, many were found to be prescribed drugs outside the recommendations for RKF.

In the Bradford & Airedale PCT population, a quarter of people aged 65 years and older had a documented eGFR <60ml/min/1.73m^2 so should have been assessed for CKD, as well as effect on any drugs they were taking. The Breton et al (2011) study also reports this finding, they had 13.3% with eGFR <60ml/min/1.73m^2, but did comment that their prevalence was lower than other reports, which may have been to do with the fact that their participants were mostly at the younger end of the age group.

3.6.3.5 Choice of kidney function estimation equation made a substantial difference to whether change of drug or dose was needed.

Using eGFR as an estimation of level of kidney function would highlight a much lower number of alterations required for drug or dose choice than would using CrCl-CG IBW. Altering or stopping drugs where needed would be missed if eGFR was used rather than CrCl-CG IBW in a large proportion of the 'patient drug events' assessed. The scoping literature review found 9 of the studies reported results as differences in use of the different equations, which ranged from 9.8% dosing errors if MDRD was used in an Italian hospital study (Moranville and Jennings, 2009), to 65% in a hospital study of nephrotoxic drugs (Cabello-Muriel et al, 2015). A primary care study in the USA found 40% of patients should have been recommended different doses (Lessard and Zaiken, 2013), and in the case-note review figures, 22% of the patients reviewed would have had different recommendations based on the equation chosen.

The results corroborate the findings from the case-note review (Chapter 1) that using eGFR as an estimation of level of kidney function would suggest a much lower number of patients needing alteration of their drug or dose than would using CrCl-CG. In the French primary care study (Breton et al, 2011), 13.7% had an eGFR <60ml/min/1.73^2 and 36.9% as calculated using the Cockcroft Gault equation, also highlighting the difference in use of the equations in an older population.

The current survey also showed that using actual weight in the Cockcroft Gault equation would mean need for alteration, or avoidance of drugs, would be missed, though to a smaller degree than using eGFR.

As discussed in the scoping review (2.6), studies found using blood levels and measured creatinine clearance to assess the equations, showed that whilst CrCl-CG underestimates by about 10% across all older ages, eGFR (calculated using the MDRD equation) overestimates as age increases by 29 - 69% (Roberts et al, 2009; Pequignot et al, 2009; Dowling et al, 2011) meaning that the safer estimate to use would be CrCl-CG. An ideal body weight, or actual if lower, should be used in the

CrCl-CG calculation to give an indication of muscle mass (BNF, 2014; Roberts et al, 2009).

3.6.3.6 Impact of not altering prescribing in RKF for the sampled drugs

- **Drugs that should be avoided in RKF.**

Alendronic acid is recommended to be avoided at levels less than 35ml/min, but a quarter of people aged 65-74 years, and over half those aged 85 years and older, had a kidney function lower than the recommended. Levels of alendronic acid in the bones are likely to be higher for these groups. Use of bisphosphonates has been increasing following guidelines for their use for primary and secondary prevention of osteoporotic fragility fractures (NICE TG160/161, 2008) which is more likely in older women. Khanal et al (2015) found alendronic acid to be one of the top 5 drugs prescribed inappropriately with 89/543 (16.3%) contra-indicated in their Australian primary care population aged ≥65 years, which can be compared to the 23.6% found in this study.

For **metformin** there were patients found with a CrCl-CG IBW <30ml/min who would be at increased risk of lactic acidosis. Metformin had the lowest figures of the 8 study drugs and this might be because of QOF and diabetes guidelines with diabetic nephropathy as a complication that is routinely looked for. Even so, a quarter of the patient drug events for diabetics aged ≥85 years had a kidney function <30 ml/min. The NICE guidelines (NICE NG28, 2015) state the recommendation of use in RKF as eGFR and it may need assessment as to whether it should be CrCl-CG IBW for older people. Below 45 ml/min level the recommendation is caution and reduce the dose; patient drug events were found where kidney function was under this level at all ages 65-99 years, and for the very old the majority were found to be prescribed for diabetics with a kidney function <45ml/min. Pillans et al (2003) looked at drugs on admission to an Australian hospital for patients with a CrCl-CG ≤40ml/min; in a total of 248 prescriptions, 44.8% were found to have an inappropriately high dose; of those, 77.3% of metformin had doses too high for their level of kidney function.

Khanal et al (2015) again found a similar level of inappropriate prescribing of metformin in Australian primary care with 3.5% (compared to 4.3% in this study) contra-indicated. Breton et al (2011) and Schmidt-Mende et al (2012) used eGFR to assess kidney function and level of CKD and so are not directly comparable, however Schmidt-Mende found a higher percentage at 8.4% inappropriate in Sweden, and Breton even higher at 15.3% contra-indicated in France.

- **Drugs where there should be a reduced dose in RKF.**

Although use of **simvastatin** has reduced with changes in recommended formulations and the reduction in cost of alternatives since the survey was run, it is still widely used. Higher blood levels of simvastatin mean that risk of side effects including rhabdomyolysis are more common, and there are alternative statins that are not affected by kidney function, such as atorvastatin. Inappropriate prescribing was found in a third of those aged 85 years and older. Statins were also assessed in the French primary care study by Breton et al (2011) who found that some were inappropriately prescribed, with 3.8% of all statins needed dose adjustment.

Fewer patients were taking **gabapentin and pregabalin** than the other study drugs, but they are at high risk from these drugs that frequently cause adverse effects (SPC). Also, use has been increasing in recent years for treatment of neuropathic pain and so numbers could be higher now. In 2013, 8.2 million prescriptions were dispensed in England for both drugs representing a 46% rise in prescribing of gabapentin and 53% rise in pregabalin prescribing since 2011 (NHS England, 2014) when this cross-sectional survey was run.

Analysis for these drugs had to be done from the dose formulation only, as dosing schedules were not possible to extract, and the recommendations are complex. This might mean that the figures are an underestimate of the number of inappropriately dosed drugs.

- **Drugs that are ineffective in RKF.**

Nitrofurantoin showed the highest figures across the age groups with the kidney function level below which it is ineffective, and ADRs are higher, is 45 ml/min. Inappropriate prescribing was found in over a third of those aged 65 years and older, and nearly 80% of the ≥85 year olds. For these patients the drug may not work increasing risk from infection, and raised blood levels increase the risk of pulmonary, hepatic, neurological, haematological, and gastrointestinal side effects during treatment (Geerts et al, 2013). A pilot investigation at one of the GP practices into use of nitrofurantoin in older patients with RKF showed that in the 22 patients with a CrCl-CG IBW <60ml/min (average CrCl 38.7ml/min), eighteen (81.8%) had further antibiotics or were recorded as still symptomatic (Howard & Wood, 2013). There has been a national strategy to use nitrofurantoin for UTI to reduce the use of cephalosporins, and because of increased resistance to trimethoprim (NICE KTT9,

2016). As UTIs are more common in older women, prescribers need help to ensure nitrofurantoin will be effective, and when to use an alternative.

A limitation of the case-note review was that it did not include non-repeat medications and this study of nitrofurantoin has shown that short course drugs can be affected. Farag et al (2014) found excess dosing of antibiotics in 64% of older people in Canada; they noted that nitrofurantoin had been prescribed when contra-indicated 169 times in the 1,464 antibiotics prescriptions studied. Many of the hospital based studies cited antibiotics as being prescribed inappropriately in RKF, for example the UK study by Jones and Bhandhari (2013) who found that antibiotics were the highest reported class. Antibiotics are widely used in primary care and need to be assessed in relation to level of kidney function.

Thiazides also do not work at low levels of kidney function, below 30 ml/min. As well as unnecessarily taking a drug that is not likely to be effective as a treatment, the patient is more at risk of adverse events such as electrolyte imbalance (SPC). This study found many older people were prescribed thiazides when they are likely to be ineffective, particularly those aged 85 years and older. Howard et al (2003) investigated reasons for preventable drug related admissions to a medical admissions unit in the UK and thiazides were one of the drug classes most frequently associated with preventable drug related admissions due to monitoring problems. They cite failure to monitor kidney function, fluid balance and electrolytes as a factor in ADRs such as over diuresis causing dehydration and renal failure.

- **Drugs where there needs to be caution in RKF because of ADRs.**

Both NSAIDs and ACEI/ARBs can cause toxicity to the kidney (SPC). This study looked at prescribing for patients on these drugs at CrCl-CG IBW <30ml/min, a low rate of kidney function leaving little reserve to cope with acute illness or nephrotoxicity.

For **NSAIDs**, there were relatively few patients found where prescribing was inappropriate in the younger age group, but over a quarter of those aged 85 years and older had a kidney function of CrCl-CG IBW <30ml/min, with a high risk to the kidney, and other adverse effects related to higher blood levels. The graph for kidney function in NSAID prescribing (Figure 22) also marks the 60 ml/min level and shows that the majority of prescribing for those aged 75 years and older had a kidney function less than 60 ml/min and would be at greater risk from their NSAID.

As discussed in the reasons for choosing to study NSAIDs (3.4.2.1), many studies have shown inappropriate use in RKF leading to ADRs, and the NICE CKD and AKI

guidelines mention NSAIDs specifically as they can worsen kidney function (NICE CG182, 2014; CG169, 2013). Guthrie et al (2011) found that 8.2% of patients aged 65 years and over with a glomerular filtration rate <60 ml/min received a 'high risk prescription' of an NSAID in their UK primary care study. The 'STOPP/START' screening tool of older people's potentially inappropriate prescriptions has several recommendations relating to NSAIDs, including to stop NSAIDs for patients '*with chronic renal failure - estimated GFR 20-50ml/min. (risk of deterioration in renal function)*' (Gallagher et al, 2008).

ACEI/ARBs were found to be prescribed for very many older people. Pillans et al (2003) looked at drugs on admission to an Australian hospital for patients with a CrCl ≤40ml/min, which would have been started in primary care. In a total of 248 prescriptions, 44.8% were found to have an inappropriately high dose; of those, 32.8% of ACEIs had doses too high for their level of kidney function. Khanal et al (2015) cited perindopril as the top drug prescribed inappropriately in high doses at 44.1%, which is high; the current study found a similar level for ACEI/ARBs in general for those aged 85 years and older (37%). Handler et al (2014) found their AKI alerts were mostly triggered by ACE/ARBs.

There is doubt about the benefits of ACEI/ARBs in very low kidney function and 'STOP-ACEi' is a currently running national multi-centre randomised controlled trial to test the hypothesis that stopping treatment with an ACEI or ARB, or a combination of both, compared with continuing on these treatments, improves or stabilises kidney function in patients with eGFR <30mls/minute (MDRD) (Bhandari et al, 2015). Although older people with RKF do not necessarily have kidney disease (Glassock and Winearis, 2009), the figures from this survey suggest further research is necessary to ensure appropriate use of ACEI/ARBs for older people.

3.6.3.7 No difference discerned between drug categories

The results tables have the study drugs listed in order of the 4 categories, but in none of the results was there any suggestion that there was a difference based on category. The differences seemed more likely to do with factors such as where monitoring is focussed and incentivised by QOF, and other initiatives such as diabetes (e.g. metformin), extent of use (ACEI/ARB high, gabapentin/pregabalin low), and where the recommendation level is at a higher level (e.g. nitrofurantoin at ≤45ml/min).

3.6.4 Strengths and limitations

Some of the limitations of the case-note review have been addressed by studying a larger population across a PCT. The study design allowed identification of prescribing with no kidney function estimation, and including the antibiotic (nitrofurantoin) meant that a drug used as a short course was included for analysis. However, this study was not able to include use of non-prescription medicines that might be significant, for example NSAIDs bought from pharmacies or retail outlets. Hopf et al (2008) found that a substantial proportion ADR-related admissions were associated with non-prescription medicines, highlighting the need for greater awareness amongst patients, prescribers and other health care professionals regarding possible serious adverse effects.

A 'complete case analysis' was undertaken for this study, recognising that biases may occur because it did not include prescribing of the drugs where the kidney function had not been tested and was not known. This effect was reduced by the fact that only a small proportion did not have a kidney function on the record.

The data for each drug was collected individually, but it is likely that some patients would be prescribed more than one of the drugs. This has meant that inferences cannot be made on the group of drugs as a whole.

Not being able to follow up any high risk cases was a limitation in the study design. No GP practice or patient level data was known so comparative analysis could not be carried out.

3.6.5 What this study adds to the literature

The prescribing for older people with reduced kidney function in primary care in a PCT has been quantitatively mapped. No other studies in this area have been found in the UK. The findings have added to the body of literature from hospitals and other countries that prescribing is not altered as recommended in RKF, and that use of eGFR or CrCl AW would mean that many older people would not have the drugs and dosing altered when evidence suggests it is required.

3.6.6 What this study adds to practice and policy

The findings will inform further research into how practice can change to reduce the risk of harm for older patients with RKF. In particular for the ≥85 year olds where, not only is the need greatest, but the population numbers are rapidly increasing so the implications from the study findings will be greater.

Issues have been raised by this survey that are important for guidelines and policy. It is known that kidney function reduces with age, and this survey showed that a quarter of ≥65s, and half of ≥85s, had an eGFR <60ml/min/1.73m^2 which needs highlighting in practice. This, and the high number of older people found to be taking renally excreted drugs, means there needs to be changes in practice to reduce the risk of harm.

3.6.7 Progression and integration of methods and findings

The PCT-wide survey built on the findings of the case-note review by testing in a wider population and addressing the need to assess extent of drug use and of kidney function testing in this population. The choice of drugs to study also came from the case-note review and use of the four categories of drugs ensured a broad picture.

When the scoping literature was updated in October 2015, many more recent studies reporting on the difference between eGFR and CrCl were found. Analysis revealed that half the studies found investigating the theoretical difference between the kidney function equations (2.6.5.10), reported using a measure of 'how many cases would have been missed'. The prescribing data from this cross-sectional survey was then re-analysed to include a 'cases missed' analysis which gives a clear measure of the impact for patients, as well as a comparison to the other studies in the literature.

The finding that a large majority of the drugs were prescribed where there was a recent kidney function test available, raised the question of why kidney function does not seem to be used when prescribing renally excreted drugs in primary care. This needed to be explored further with prescribers.

3.7 Conclusion

Prescribing recommendations in RKF were not followed for a large population of older people in a Primary Care Trust. For all the study drugs, and for all age bands, there was prescribing of the drugs found where the kidney function was too low for recommended use. The numbers of older people found taking the study drugs were large, meaning that many patients could be at risk of harm. The Bradford population

has a lower proportion of older people than the national average which could mean that the findings might be an underestimate for the wider population.

From the literature review findings, the case-note review, and cross-sectional survey, there is a need for a qualitative enquiry to understand the determinants for why prescribers do not apply the recommendations for prescribing in RKF in primary care.

"Decision making is … something which concerns all of us, both as maker of the choice, and as sufferers of the consequences."

D. Lindley 1971

4 Chapter 4: A qualitative GP interview study to explore why prescribers do not apply prescribing recommendations for older people with reduced kidney function.

4.1 Background

Risk of harm and hospital admission are increased for older people when drug licence recommendations for prescribing in reduced kidney function (RKF) are not applied, as revealed in the scoping literature review (Chapter 2). Kidney function reduces with age but it is not always accounted for by prescribers in primary care, as found in the case-note review (Chapter 1) and the PCT-wide survey of prescribing data (Chapter 3).

No research evidence was found in the scoping literature review (Chapter 2) on why prescribers do not apply the recommendations for prescribing of medicines where kidney function is reduced. Where prescribing errors in general have been explored, the causes and associated factors have been found to be numerous (Slight et al, 2013) with a complexity that would mean solutions addressing only one factor (such as lack of knowledge) would be likely to have only limited benefit (Tully et al, 2009).

As introduced in Chapter 1 (1.4), where behaviour needs to be changed, it is more successful if an intervention is developed on evidence-based principles of behaviour change (Cane et al, 2012). Using a theoretical approach allows identification of factors and strategies that are more likely to be effective (Nilsen, 2015). The scoping review found a lack of theoretical underpinning in the studies aiming to improve prescribing in RKF (Chapter 2, 2.6), which might be a factor for the lack of benefit found in many of the trials if the intervention was not addressing the barriers, and provides no understanding of the determinants where a positive outcome was shown.

To inform an intervention that is likely to be successful in improving recommendation application and reduce risk for patients, there needs to be a systematic exploration to understand prescribing for older patients with RKF by general practitioners (GPs) in the care pathway (the 'behaviour').

This study aimed to explore why GPs do not apply the drug licence recommendations when prescribing for older people with RKF.

4.2 Research question and objectives

Research question

Why are prescribing recommendations not applied for older people with reduced kidney function in primary care?

Objectives

- To systematically identify the potential barriers and enablers to prescribing appropriately in reduced kidney function using the Theoretical Domains Framework (Michie et al, 2005; Cane et al, 2012) to understand whether prescribers have the capability, opportunity, and motivation in the care pathway (Michie et al, 2011).

- To identify what needs to change in the factors affecting the care pathway to improve implementation of the prescribing guidance.

4.3 Methodology

4.3.1 The behaviour

The World Health Organisation describes a systematic stepped approach to prescribing (de Vries et al, 1994):

1. Define the patient's problem.
2. Specify the therapeutic objective.
3. Verify the suitability of the drug, the most effective, safe, suitable and cheap option.
4. Write a prescription.
5. Give information, instructions, and warnings.
6. Monitor (and stop?) the treatment.

A reduced kidney function would need to be part of the prescribing decision process at Step 3 as to whether there are any recommendations for prescribing in RKF that would mean a drug is 'unsuitable', and whether it would be 'unsafe' unless a reduced dose, or alternative were used. It would also impact on Step 6 as kidney function can change, and so it would need monitoring to ensure the drug and dose is still suitable. The level of kidney function would need to be considered at initiation of a drug, medication review, and whenever circumstances change, such as acute admission, infection or starting another nephrotoxic drug.

Three of the four aims of good prescribing described by Barber (1995) similarly state that the prescriber should maximise effectiveness, minimise risks, and minimise costs, both on first prescribing a drug and on subsequently monitoring it. The fourth additional aim stated is to respect the patient's choices (Barber, 1995). The recent guidelines on medicines optimisation reiterate the aim to ensure that the 'right patients get the right choice of medicine at the right time' (Royal Pharmaceutical Society, 2013).

Multiple other influences such as guidelines for prescribing in specific clinical conditions, for example NICE, drug formularies leading drug choices, and national strategies such as use of antibiotics, add in to make the factors determining this behaviour highly complex.

As introduced in Chapter 1 (1.4) 'COM-B' (Figure 25) is a model which recognises that behaviour is part of an interacting system involving capability, opportunity and motivation (Michie et al, 2011). Interventions need to change one or more components in such a way as to put the system into a new configuration and minimise the risk of it reverting. Understanding the behaviour in context will highlight what needs to change (Michie et al, 2014).
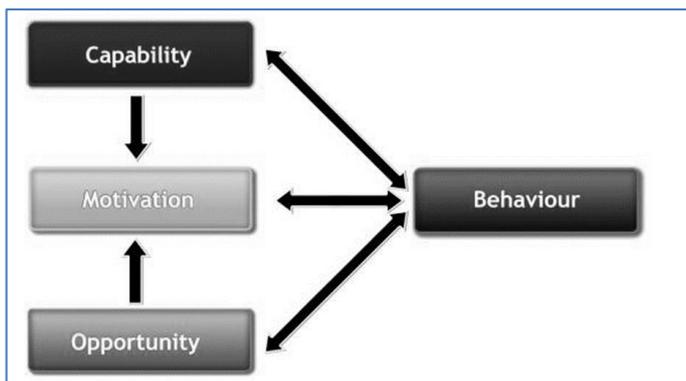
Figure 25: The COM-B model - a framework for understanding behaviour (Michie et al, 2011).

Use of the COM-B model highlights questions about the behaviour of prescribing when kidney function is reduced.

Capability

- Do prescribers know that some drugs need assessment of level of kidney function to advise their use or level of dose?
- Do prescribers know how to apply the recommendations?

- Do prescribers know about the different estimation equations and how to use them appropriately?
- If they know about the recommendations, do they remember to apply them?
- Do prescribers have the skills needed to assess kidney function in relation to prescribing?

Opportunity

- Is the environment conducive, both physical and social?
- Are there resources available to help prescribers apply the recommendations?
- Does the patient record system help, or hinder, appropriate prescribing?

Motivation

- Are there intentions, and/ or conscious goals to prescribe appropriately in RKF?
- What habits or impulses are involved in the process?
- Are factors regarding the professional role relevant?
- What are the beliefs of prescribers about the consequences of prescribing appropriately, or not, in RKF?

4.3.2 The Theoretical Domains Framework (TDF)

Michie et al (2014, p93) describe how a more detailed understanding of the behaviour can be gained by using the TDF to expand on the COM-B components, and Table 5 in Chapter 1 shows how the TDF domains link to COM-B and which provided the framework for the exploration in this study.

Chapter 1 (1.4) introduced that changing behaviour is more effective if interventions are developed on evidence-based principles of behaviour change (Cane et al, 2012). Two main issues have been identified as reducing the likelihood of success of implementation strategies (Dyson et al, 2011);

- A failure to identify barriers and enablers to implementation of evidence based practice (Grimshaw et al, 2004; NICE, 2007).

- A lack of theoretical basis for the interventions used to support the implementation of evidence into practice (Grimshaw et al, 2004; Michie et al, 2005).

There are many theoretical models to explain behaviour change with multiple contending theories, and Michie et al (2005) have highlighted that such a large number of theories and theoretical constructs cannot be fully applied, and there was a need for a method to select among them. The TDF has addressed the need for an overarching

determinant framework and was developed to identify individual factors known to influence the gap between evidence based practice and the routine delivery of health care. The TDF is an integrative framework synthesising key theoretical constructs used in relevant theories. The scoping literature review (Chapter 2, 2.6) found a lack of theory underpinning the intervention studies suggesting the need for a comprehensive framework to consider all relevant theories.

Originally, the synthesis of 128 constructs related to behaviour change, found in 33 behaviour change theories, were developed into 12 domains, such as knowledge, skills, goals, and beliefs about capabilities (Michie et al, 2005). The constructs were then validated and restructured to 14 domains in 2012. (Cane et al, 2012; Michie et al, 2014). The 14 TDF domains have been linked to the COM-B components by Michie et al (2014, p92) (Table 5, Chapter 1).

In the scoping literature review, no evidence was found on the determinants for prescribing in RKF, but the TDF has been used to identify key theoretical domains that are perceived to influence healthcare professionals and their prescribing. Cadogan et al, (2015) found that all the theoretical domains, except 'Emotion', were considered relevant to the target behaviour of 'prescribing of appropriate polypharmacy in primary care', which illustrates the complex nature of the behaviour as well as the challenge faced by the researcher when developing interventions for change. Duncan et al (2012) explored beliefs among trainee doctors, including that prescribing errors were not likely to have consequences for patients, and found that seven theoretical domains were relevant: social professional role and identity, environmental context and resources, social influences, knowledge, skills, memory, attention, and decision making, and behavioural regulation. Potentially important domains were beliefs about consequences and abilities which could be targeted for an intervention.

4.3.3 Study design methodology

Face-to-face semi-structured interviews were chosen to allow each participant to talk in depth about particular issues and focus on individual experiences, follow up of interesting responses, and investigation of underlying motives. Non-verbal cues may add to understanding the verbal response, and franker responses may be possible if participants are not with their peers (Robson, 2011). The TDF has been used in interview studies for topic guides and analysis, for example, Francis et al (2009), who used methods based on theoretical construct domains to understand clinicians' blood transfusion behaviour, and Dyson et al (2011) who used the theoretical approach to explore hand hygiene behaviour.

An ethnographic approach would have allowed actual behaviour to be observed but not access to attitudinal data, which would be important for an exploration of the decision making process. Also, the cross-sectional prescribing data survey suggested that assessment of kidney function when prescribing did not happen and so a method is required that can explore more than what can be observed. Themes were not yet known to create an appropriate questionnaire and it would have been unlikely to provide the depth needed or the opportunity to investigate responses further. A focus group may have been the method of choice to seek a broad range of ideas (Green and Thorogood, 2009), but would not give an in-depth exploration of individual experience, and individuals are less likely to disclose errors or bad practice.

4.4 Method

4.4.1 Research team

4.4.1.1 Personal characteristics

The one researcher, and interviewer, for this study was myself as a female pharmacist (BPharm PG Dip MPharm) and PhD student, overseen by the supervisory team.

Training gained to inform the setting up of the study, data collection and analysis:

- University of Leeds School of Healthcare Research Methods Module.
- Leeds Institute for Health Sciences Health Research: module 2: capturing data for research, and module 3: handling data for research.
- Health Services Research & Pharmacy Practice Conference seminar by Professors S. Michie and M. Johnstone (Aberdeen, 2014).
- UK Society for Behavioural Medicine day workshop by Dr L. Atkins (Nottingham, 2014)

Experience: this was the first structured research interview study conducted, informed by over 20 years of professional interviewing experience as a practitioner. The conducting of the interviews was mentored by Professor R. Foy, and the analysis by Dr C. Easthall, both experienced in qualitative research and behaviour change theory.

4.4.1.2 Relationship with participants

The letter of invite established that the research would be conducted by a pharmacist who was also reading for a PhD (Appendix 8, 8.6). It was made clear at the start of each interview that it was being conducted by a pharmacist with a particular interest in prescribing in RKF. It was expected that some of the participants may know the interviewer professionally, and/or may have heard her talk on the subject. This was therefore asked, and noted as part of the demographic data collected to inform the analysis.

4.4.2 Study design

4.4.2.1 Theoretical framework

The theoretical domains framework, as an integrative framework synthesising key theoretical constructs used in relevant behaviour change theories, informed the development of the interview topic guide and analyses framework.

4.4.2.2 Participant selection

Sampling

General Practitioners were purposively sampled to give a range of length of time as a prescriber and whether they were a GP trainer. At least 2 participants would be recruited from each of the categories <8 years prescribing experience, 8-18 years, and >18 years, and at least two for each of GP trainer and non-trainer. The original plan had been to use categories for length of time as a prescriber as <5, 5-15, >15years, but meeting the first registrar participant made it clear that by the time doctors start GP training they will have had more than 5 years prescribing. Changing the categories would give a more realistic spread of prescribing experience in primary care.

Method of approach

Invitation packs were delivered to GP practice 'pigeon holes' by the local practice pharmacist team as a known and trusted route of access.

Potential participants received a research study pack containing a letter of invitation (Appendix 7, 8.6), consent form (Appendix 8, 8.7) and information sheet (Appendix 9, 8.8). One follow-up email was sent where no reply had been received.

A certificate of attendance was provided for all interviewees as a recognition of their participation in research (Appendix 10, 8.9).

Sample size

The number of GPs recruited for interview was dependent on when data saturation was reached, defined as no new themes or concepts elicited. Following the recommendations for interview studies that use a theory-based content analysis by Francis, Johnstone et al (2012), the criteria for data saturation for this study were:

- Initial analysis sample: at least 10 interviews would be conducted (with diversity sampling to ensure the sample covers the inclusion criteria for prescribing experience and trainer status).

- Stopping criterion: when 3 further interviews had been conducted with no new themes emerging in each of the TDF domains, this would be defined as the point of data saturation.

Non-participation

Non-participation rates, and the reasons, were collected.

Pre-interview reading

Participants were sent a short document by email to read prior to the interview (Appendix 11, 8.10). This pre-reading gave a short summary of the findings of the project so far and examples of drugs that should be avoided, dose reduced or are ineffective, to allow them to think about some of the issues before the discussion. The extent of older people on drugs that were not appropriate for their level of kidney function in the PCT-wide cross-sectional study (Chapter 3) suggested that many prescribers may not have thought about the issues. The pre-reading would allow them to consider the results in relation to their own practice and experience to inform the discussion.

4.4.2.3   Setting

This study was based in Bradford Districts Clinical Commissioning Group (CCG), encompassing 47 practices. CCGs superseded the former PCTs to organise the delivery of NHS services in England. Bradford Districts CCG was the larger part of the former Bradford & Airedale PCT where the cross-sectional PCT-wide prescribing data survey was run (Chapter 3), and so the interviews would be with GPs prescribing in the same setting. This would mean that the quantitative findings could be explored with the prescribers involved, but does mean that views from a wider context would not be captured.

4.4.2.4   Data collection

Semi-structured, individual, face-to-face interviews were conducted. A topic guide (Appendix 12, 8.11), with theory-based prompts based on the TDF, was used to explore attitudes, beliefs, enablers and barriers. It also aided exploration of prescribing different drugs for older patients with RKF, and what needs to change in the factors affecting the care pathway to improve implementation of the prescribing guidance. Open questions were used to elicit personal experience and explore responses further (Green et al, 2011). All the interviews were conducted by myself, introduced as a pharmacist but acting as a researcher for this study. Only one interview was conducted for each participant.

The topic guide was developed with input from the supervisory team. It had been planned to pilot test the topic guide, but it had to be cancelled before the first interview date. The first interview was therefore used as a pilot, and if any major changes were

needed then it would have resulted in the transcript not being used for the final analysis.

Interviews were audio-recorded with permission; field notes were made after each interview. Any information that could lead to a participant being identified was removed at the transcription stage and an identification code applied. Transcription was done by an administrator and checked by myself for accuracy. The data was managed using N-Vivo QSR v10.

4.4.3 Analysis

4.4.3.1 Demographic analysis

A standard form was constructed to collect demographic data for each participant on length of time as a prescriber and whether they were a GP trainer. Also noted were gender, any special interests and whether the participant knew me and/or had heard me speak on prescribing for older people with RKF. Whether a participant had heard me discuss prescribing in RKF was noted so that any difference in themes could be analysed.

4.4.3.2 Data saturation analysis

The data saturation analysis was conducted in four steps (Francis, Johnstone et al, 2012):

1. Data tables were constructed for themes in each theoretical domain elicited for each individual.
2. Summary tables were constructed for each domain (knowledge, skills etc.) with themes mentioned by each participant interviewed.
3. Data from the summary tables were used to construct cumulative frequency graphs, displaying sequentially numbers of new themes elicited in each domain.
4. The cumulative frequency graphs were inspected to investigate when the stopping criterion had been met (set at 3) for each domain and overall.

4.4.3.3 Content analysis

A theory-based, five stage content analysis was conducted (Pope et al, 2000). A second researcher (CE) was involved to explore inter-rater reliability by coding the first 2 participant transcripts, and providing discussion where needed. CE is a pharmacist experienced in behaviour change theory, and with both content (prescribing) and methodological (qualitative research) expertise. A third person (EW) helped with identification of emerging themes and charting the data; as a social scientist and non-pharmacist she brought a new perspective to help elucidate meanings.

Stage 1. Familiarisation

Interview recordings were listened to and transcripts read and re-read to become familiar with the data, and get an initial impression of the key ideas and recurrent themes.

Stage 2. Identifying a thematic framework

The coding index was applied systematically to all the data by annotating the transcripts. I coded all the transcripts and then met again with CE to discuss any issues that were unclear and verify the findings. An example is the first page of the P1 charting, shown in Table 37.

Stage 3: Indexing

The key issues, concepts and themes by which the data would be examined and referenced, were identified from the a-priori Theoretical Domains Framework (TDF), and the views or experiences from the data. For the first participant (P1), both researchers (myself and CE) coded independently to the TDF. The two researchers then met to review the coding and agree on any discrepancies by discussion.

P2 was coded independently by both researchers, who then met again to review; this time there were fewer discrepancies to discuss. A coding index was developed.

Stage 4. Charting

The codes and quotes were manually grouped into emerging themes (Figure 26) with the help of EW. This was an iterative and reflective process and allowed exploration of intra-rater reliability by re-visiting and refining the coding.

	Theme	Representative quotes
Knowledge	Awareness of need to take action	• I am more aware of it now than I used to be • I am aware of it if I'm starting a new drug • The initial thing would be education…everybody who is training or everybody who is trained, just to be made aware that there is an issue, that they need to be careful to look for renal function when they prescribe a new drug or when renal function deteriorates
	Lack of knowledge about prescribing in RKF	• I suspect for some clinicians and I include myself in that, maybe a knowledge er gap as well you know • I can't think there are clinicians who are wilfully doing that [prescribing wrongly], erm', but is more that they just don't know
	Deficits in clinicians training	• when I was initially prescribing I don't think renal function would have been hugely on my agenda • You talk to medical students now and they don't have any dedicated pharmacology lectures
Skills	Use of a formulary	• when you are putting a new drug on and the eGFR is less than 60, you should probably looking to see whether or not there is a note in the formulary on that.
	Checking kidney function	• if you click on to their renal function when you are putting a new drug on and the eGFR is less than 60,
Social/professional role and identity	Perceived duty/role	• …longer term monitoring, I suppose that falls into the area of what people like yourself and Y do isn't it?

Table 37: Charting to TDF domains for P1- first page.

Figure 26: Charting the codes and quotes and then mapping and interpretation to define 'key themes'.

- Motivation and goals ➝ intentions) both in reflective motivation
  ➝ goals) so don't need to re-analyse

- Behavioural regulation – focuses on self-regulatory processes

- Beliefs about capabilities ➝ belief about capabilities) both reflective motivation
  ➝ optimism) so don't need to re-analyse

- **Beliefs about consequences** ➝ Beliefs about consequences – reflective motivations
  'pure beliefs'
  ➝ Reinforcement – automatic motivation
  'associative learning'

- **Nature of the behaviours removed** – need to re-analyse

Figure 27: Re-mapping and analysis needed to the updated domains on the TDF.

Stage 5. Mapping and interpretation

When categorising for what needed to change in capability, opportunity and motivation (Michie et al, 2014), the 'Behaviour Change Wheel' used the updated TDF version that had 14 domains, with some changes to the existing categories. The re-mapping of the

coding needed is shown in Figure 27; recoding was required for the 'nature of the behaviours' and to split 'beliefs about consequences' onto new domains.

The emergent themes were mapped and interpreted under each TDF domain, categorised under capability, opportunity and motivation to structure the findings on what needs to change (Figure 26). The themes were charted in Excel and analysed for numbers and differences with participant type. A summary of the themes was developed for each of capability, opportunity and motivation.

The range and numbers of themes was explored using Excel to give an indication of the frequency of discussion by participants in terms of:

- The number of participants mentioning a theme in each domain.
- The number of different themes identified in each domain.
- The total number of different themes mentioned by all the participants in each domain.

4.4.3.4 Identification of key themes

This study had a qualitative design, and the interviewees were recruited to give a sample with a wide range of expertise and experience, rather than to be a representative sample. The aim was to identify the range of potentially influential determinants, decipher the content and nature, and enable future analysis of hierarchy to determine prioritisation for intervention. The identification of 'key themes' therefore aimed to be a synthesis of the range of themes elucidated, noting where themes were frequently mentioned, prominence of themes both from number and intensity, and also where there might be high importance for an intervention, even of only mentioned by one interviewee.

The themes and quotes in each domain were read and re-read and the common, and important, research themes were identified as 'key' in what needs to change to improve prescribing for older people with RKF. The 'key themes' of associated determinants across domains and COM-B categories were developed from:

- The TDF domains with the highest number of different themes elucidated.
- The themes most discussed by participants.
- Themes that might not have been frequently brought up by participants, but that would be likely to be important, influential and have high impact.
- The summaries of what needed to change for greater capability, more opportunity and stronger motivation.
- Common strands across the COM-B components.

Having drafted the 'key themes', they were reviewed back with the original set of
themes and quotes under each domain to confirm that the most important findings had
been included.

4.4.4 Ethics and governance

University ethics (SHREC/RP/346 on 27/6/13, Appendix 13, 8.12), NHS governance
assurance (on 5/11/13, Appendix 14, 8.13), and letter of access (Appendix 15, 8.14)
were granted. NHS ethics approval was not needed as participants were healthcare
professionals.

4.5 Results

4.5.1 Recruitment

Fifteen GPs were interviewed. Recruitment packs had been delivered to 72 GP pigeon
holes in 26 GP surgeries. Overall there were 21 positive responses (29.2%) which
resulted in 15 interviews; 2 had to decline because of lack of time and 4 were not
pursued as data saturation had been reached (Figure 28). Fifty-one did not respond to
the invitation.
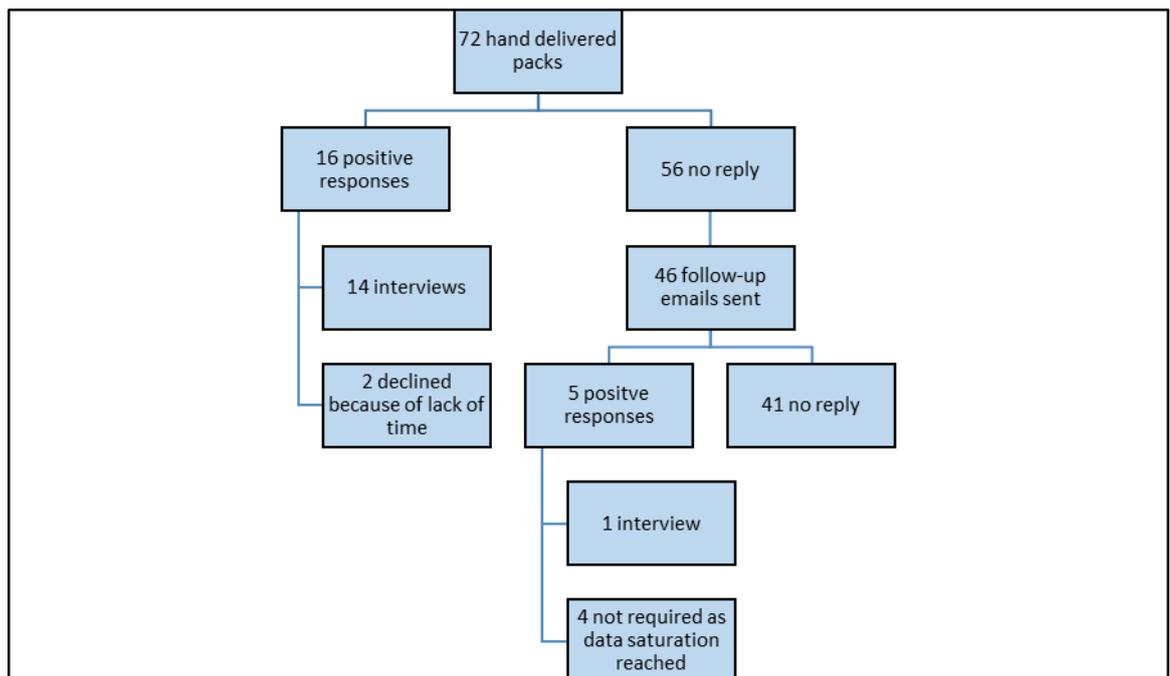
Figure 28: Responses resulting from the participant recruitment

4.5.2 Demographic analysis

The GPs had 7-32 years prescribing experience. Nine were GP trainers. In the first 10
participants (initial analysis sample) there was only 1 who had less than 8 years

prescribing experience so at least one more needed to be recruited to represent adequate diversity defined by the inclusion criteria. Table 38 gives a summary of the participant characteristics. Twenty-three wide-ranging specialities were represented in the sample including neurology, diabetes, mental health, drugs safety and education.

Interviews took place between January and April 2014, and were conducted at GP practices, except one at a community hospital. Nobody else was present in the interviews except the interviewer and participant. Interviews all lasted 35-45 minutes.

The audio-recording failed when interviewing P3 so no transcript was available for content analysis. Notes were written as soon as the recording failure was realised (later the same day).

4.5.3 Data saturation analysis

Data saturation was reached after 12 interviews. No new themes were elicited from the final three interviewees, who were one from each 'length of experience' category. Excel tables were used to collate and assess the themes elicited in each domain, and presented in the following sections (Tables 40 - 45).

Figure 29 shows the cumulative themes elicited per TDF domain sequentially as the interviews were completed and analysed. After 10 recorded interviews the initial analysis sample yielded 113 themes in total. Data saturation had not been reached for 6 of the domains; this, as well as needing at least one more participant with <8 years prescribing experience, meant that further participants were recruited.

participant	gender		time as a prescriber			GP trainer		knew the researcher?			particular interests
	female	male	<8yrs	8-18yrs	>18yrs	yes	no	did not know me	knew me but not heard me on drugs and RKF	knew me and heard me on drugs and RKF	
P1		▓		▓		▓		▓			Ear/nose/throat GPwSI, men's health, respiratory, prescribing lead
P2	▓		▓				▓	▓			registrar
P3	▓				▓	▓		▓			elderly care
P4		▓		▓		▓		▓			respiratory; patient safety
P5	▓			▓			▓			▓	education
P6	▓			▓			▓			▓	neurology GPwSI
P7	▓			▓			▓			▓	general med; paediatrics; elderly
P8		▓		▓		▓				▓	diabetes GPwSI
P9	▓			▓		▓				▓	Musculoskeletal; mental health
P10	▓		▓				▓			▓	gastroenterology; diabetes
P11	▓		▓				▓			▓	diabetes; undergraduate education
P12	▓				▓		▓			▓	women's health
P13	▓			▓			▓			▓	women's health; epilepsy
P14		▓			▓	▓				▓	GP appraiser; mental health
P15	▓		▓				▓			▓	registrar; women's health

Abbreviations: GPwSI: GP with Special Interest; RKF: reduced kidney function.

Table 38: GP interviewee characteristics.
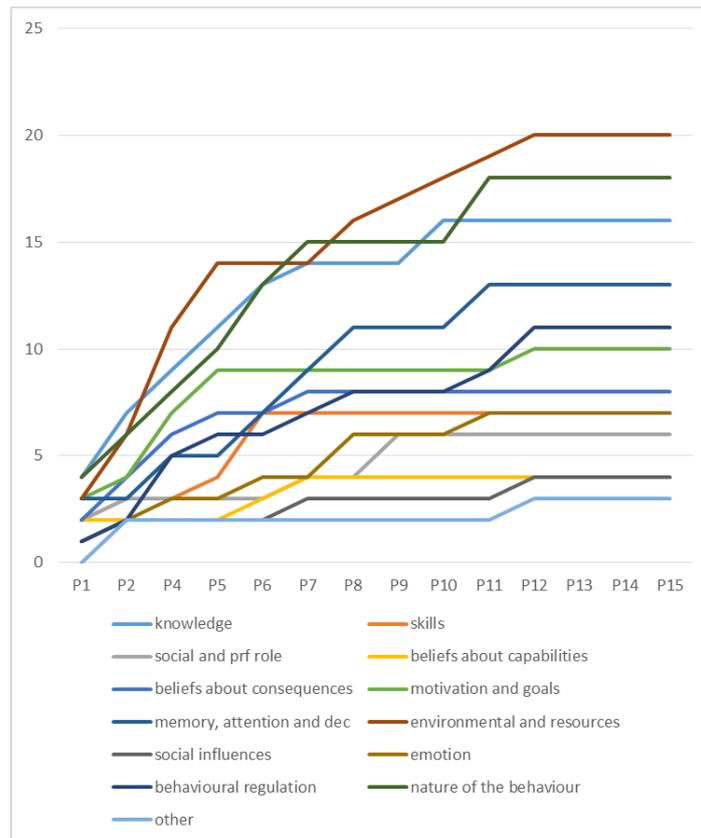
Figure 29: Themes elicited per domain summary data for saturation analysis.

The 15th participant was a registrar with <8 years' experience and so the analysis was then re-run. At that point there were a total of 127 themes elicited, and no new themes from P13, 14 or 15. It was concluded that data saturation had been reached for themes on experience in prescribing for older people with RKF.

4.5.4 Theory-based content analysis

The data was analysed to explore the barriers and enablers when prescribing for older people with reduced kidney function to find out if greater capability, more opportunity or stronger motivation is required (Michie et al, 2014).

4.5.4.1 Analysis of themes

Excel tables were used to collate and assess the themes elicited in each domain, and are presented in the following sections. The tables were used to visualise when data saturation had been reached, and to analyse differences with participant type. The tables have also allowed an exploration of the themes in terms of frequency of discussion by interviewees, which has been summarised in Table 39, ordered by total number of themes discussed by the participants.

	number participants mentioning a theme in the domain	number of themes found	total number of themes mentioned by participants	theme most mentioned
environment and resources	14	20	69	there are competing priorities and time constraints
knowledge	14	16	56	there is a lack of knowledge about specific drugs
memory, attention and decision	12	13	52	it is difficult to remember to do, and which drugs
beliefs about consequences	14	9	34	RKF can cause toxicity from the drug, and to the kidney
motivation and goals	13	10	27	a motivation is to not do harm
nature of the behaviour	9	18	25	eGFR is used to assess kidney function
skills	13	7	22	the skill is difficult to do
behavioural regulation	12	11	20	want computer decision support
beliefs about capability	13	5	16	there is a lack of confidence in capability
emotion	11	7	15	stressed/worried/bothered if not doing it correctly
social/prof role	9	6	11	peer discussion is useful
social influences	9	5	10	pharmacist influence is valued

Abbreviations: eGFR: estimated glomerular filtration rate; RKF: reduced kidney function.

Table 39: Summary of frequency of themes discussed by interviewees, ordered by the total number of themes mentioned by the participants.

Themes were found across all the TDF domains, with at least 9 of the interviewees discussing issues in every domain. Themes on 'knowledge', 'environment and resources', and 'beliefs about consequences' were mentioned by all 14 interviewees recorded. The domains with the greatest number of themes from the interviewees were:

- Environment and resources
- Knowledge
- Memory, attention and decision process
- Beliefs about consequences
- Motivation and goals

4.5.4.2   What needs to change for greater capability?

Figure 30 shows the barriers and enablers found on what needs to change for greater capability.

Psychological capability

Table 40 shows the three tables developed to chart the themes in the domains for psychological capability:

Knowledge

Memory, attention and decision process

Behavioural regulation.

Capability

Physical	Psychological

Enablers

		to draw attention to warnings at the medication review and to the relevant drugs	GPs are cautious when prescribing
			caution when prescribing for older patients
		understanding 'why' makes easier to remember	have a rule to follow
		warning available when initiating a drug	to have a kidney function test done before a medication review
		computer decision support	
easy to do once learnt what to do	understanding the relationship between kidney function and the effect on drug blood levels/ effect	trigger to remind	reinforcment/ repeating the message
embed as part of the prescribing process		triggers: instruction, crisis, old age of patient, reduced kidney function, known drugs	education changes practice
easy to check kidney function	teaching by a pharmacist		learning about a specific drug changes practice

Skills	**Knowledge**	**Memory, attention & decision process**	**Behavioural regulation**

Barriers

not within the current prescribing process	poor insight into appropriateness of prescribing in RKF	having to remember which drugs and the recommendations for each	habit of prescribing the 'usual' dose that is always prescribed
multi-step process		attention elsewhere in the consultation	would forget if not reinforced/ repeated
polypharmacy makes it complex	lack of knowledge about recommendations, why needed and about kidney function estimates for prescribing	not thought of at the medication review	
not knowing what to do to calculate a kidney function estimate and recommendation application	Lack of knowledge even if prescribing the drug regularly or an expert in the field	not got warnings at the medication review	
		insufficient triggers	
having a kidney function estimate but not applying to drugs	not taught, either theory or skills		

Figure 30: Perceptions of barriers and enablers for what needs to change for greater capability.

Knowledge domain

Participant	M/F	Length of prescribing experience (<8yrs=1, 8-18yrs=2, >18yrs=3)	GP trainer Y/N	Knew me/heard me (NN, YN, YY)	knowledge	Awareness of need to take action	Aware of need to take action more than used to be	Some awareness of eqns to estimate kidney function for prescribing	eGFR not reliable in older people	learning in elderly medicine helpful	more familiar with the issue related to diabetes drugs	knowledge of computer tool	Knowledge gap	Lack of knowledge about specific drugs	Lack of knowledge about specific drugs despite being expert in the clinical area	Lack of knowledge about specific drugs despite regular prescribing	Lack of knowledge about CrCl CG	Lack of medical student knowledge about drugs	pharmacology at med school	Prescribing in reduced kidney function not taught	Learn once practising	number of different knowledge themes mentioned per participant
P1	M	2	Y	YN	✓	✓	✓						✓							✓		4
P2	F	1	N	NN	✓									✓		✓			✓	✓	✓	5
P4	M	2	Y	NN	✓				✓					✓		✓		✓				4
P5	F	2	N	YN	✓	✓						✓							✓			3
P6	F	2	Y	YN	✓	✓								✓		✓			✓	✓	✓	6
P7	F	2	N	YN	✓	✓					✓			✓					✓	✓		5
P8	M	3	Y	YY	✓				✓		✓											2
P9	M	2	Y	YY	✓		✓											✓				2
P10	F	2	Y	YN	✓					✓			✓						✓		✓	4
P11	F	2	N	YY	✓	✓								✓		✓	✓	✓	✓		✓	7
P12	F	3	Y	YY	✓		✓												✓			2
P13	F	2	N	YY	✓	✓	✓					✓		✓	✓				✓		✓	6
P14	M	3	Y	YN	✓			✓	✓	✓				✓					✓			4
P15	F	1	N	NN	✓			✓					✓									2
Number of participants mentioning the theme					14	6	4	2	3	2	3	2	3	7	1	4	1	3	7	3	5	56

Memory, attention and decision process domain

Participant	M/F	Length of prescribing experience (<8yrs=1, 8-18yrs=2, >18yrs=3)	GP trainer Y/N	Knew me/heard me (NN, YN, YY)	Memory, attention and decision process	Difficult to remember	Easier to remember when do more often	Attention directed elsewhere	Doesn't think of it at med review	More attention when starting a new drug	Instruction helps	trigger: crisis	trigger: old age	trigger: RKF	trigger: specific drugs	Not got at med review	Warnings	Want more decision support	number of different knowledge themes mentioned per participant
P1	M	2	Y	YN	✓	✓			✓									✓	3
P2	F	1	N	NN															0
P4	M	2	Y	NN	✓	✓								✓			✓		3
P5	F	2	N	YN	✓													✓	1
P6	F	2	Y	YN	✓						✓		✓					✓	3
P7	F	2	N	YN	✓	✓		✓	✓	✓			✓				✓		6
P8	M	3	Y	YY	✓		✓			✓		✓	✓	✓					5
P9	M	2	Y	YY	✓	✓	✓	✓		✓	✓								5
P10	F	2	Y	YN	✓	✓				✓				✓				✓	4
P11	F	2	N	YY	✓	✓	✓	✓	✓	✓			✓	✓	✓	✓	✓	✓	11
P12	F	3	Y	YY	✓	✓			✓	✓				✓			✓	✓	6
P13	F	2	N	YY	✓			✓	✓									✓	3
P14	M	3	Y	YN	✓	✓												✓	2
P15	F	1	N	NN															0
Number of participants mentioning the theme					12	8	3	4	5	6	2	1	4	5	1	1	4	8	52

Behavioural regulation domain

Participant	M/F	Length of prescribing experience (<8yrs=1, 8-18yrs=2, >18yrs=3)	GP trainer Y/N	Knew me/heard me (NN, YN, YY)	Behavioural regulation	Caution related to the behaviour	Things should change/will change	Education needed	need a rule to follow	need computer decision support	need KF test result before the med review	read up on the area	pharmacist teaching has changed practice	reinforcement of message helps	learning about a specific drug has change practice	computer alerts	number of different knowledge themes mentioned per participant
P1	M	2	Y	YN	✓			✓									1
P2	F	1	N	NN	✓						✓						1
P4	M	2	Y	NN	✓		✓			✓						✓	3
P5	F	2	N	YN	✓		✓			✓							2
P6	F	2	Y	YN	✓					✓		✓					2
P7	F	2	N	YN	✓	✓		✓									2
P8	M	3	Y	YY	✓	✓									✓		2
P9	M	2	Y	YY	✓			✓		✓							2
P10	F	2	Y	YN													0
P11	F	2	N	YY	✓									✓			1
P12	F	3	Y	YY	✓					✓			✓				2
P13	F	2	N	YY	✓				✓								1
P14	M	3	Y	YN													0
P15	F	1	N	NN	✓							✓					1
Number of participants mentioning the theme					12	2	2	3	1	5	1	2	1	1	1	1	20

Abbreviations: CrCl CG: creatinine clearance Cockcroft Gault; M/F: male/ female; RKF: reduced kidney function; Y/N: yes/ no.

Table 40: Psychological capability: charting themes in 3 TDF domains

The knowledge domain had themes from all interviewees, and the second most total number of themes discussed. The 'memory, attention and decision process' domain was the third most discussed.

Knowledge

There was little awareness of the need to alter prescribing for the majority of participants when prescribing renally excreted drugs if kidney function was reduced.

"It's probably one of those areas where there is a bit of a blind side." (P4)

"I can't think there are clinicians who are wilfully doing that [prescribing wrongly], *erm, but it is more that they just don't know."* (P1)

Two participants thought that their awareness had increased recently with increased use of nitrofurantoin and the MHRA Drug Safety alert on use in RKF.

"I am more aware of it than I used to be." (P10)

"Nitrofurantoin wasn't coming up on my radar at all until about a year ago." (P9)

Lack of knowledge was widely expressed, with 11 of the 15 participants mentioning it without prompting, having read the pre-interview information.

"I suspect for some clinicians, and I include myself in that, there may be a knowledge gap." (P1)

Inadequate knowledge about prescribing specific drugs in RKF was conveyed, even those that are regularly prescribed or where the GP had a clinical expertise:

 "I wasn't really aware of gabapentin and pregabalin erm, or simvastatin actually." (P11)

 "I wasn't aware. This is terrible because I use a lot of gabapentin and pregabalin, obviously, in neurology." (P6)

Very little knowledge was expressed about the Cockcroft Gault kidney function estimation equation.

"I would have no idea, cos everything that I do currently is with eGFR." (P2)

It was mentioned that medical students have little knowledge about drugs in general.

"It's amazing, no, they [medical students] *don't know anything about drugs." (P6)*

"The knowledge of medical students is very, very minimal, you know. They don't know the different drug names, groups of diuretics, you know. You ask them about what group is such and such and they just don't know." (P14)

Prescribing when kidney function is reduced has not been taught. The two registrars were still in training and had not had teaching on this area.

"..but is it something we are specifically taught? No." (P2)

"As a GP trainee there certainly hasn't been a teaching session on the kidney – reduced kidney function." (P15)

Two participants highlighted a difference between the recommendation for drug use in RKF versus clinical guidelines; one on the use of nitrofurantoin, and the other anti-hypertensives.

"Although we are supposed to avoid so many other antibiotics now, it kind of sometimes – nitrofurantoin could be really useful." (P2)

"How many of our elderly patients with their high blood pressure would do better because they would stop falling down, or would do worse because actually we'd never get the blood pressure under control because the maximum dose we'd be using would be lower." (P2)

The participant's view was that these examples were goal conflicts. However, in both cases, it was a lack of knowledge and understanding of the implications of RKF on drug blood levels that led them to their views. Nitrofurantoin would not be useful when trying to avoid other antibiotics in RKF because it would be likely to be ineffective. The reason the recommended maximum dose of the anti-hypertensive is reduced is because RKF would lead to increased blood levels so the dose needs reducing to achieve the same blood levels as someone with normal kidney function.

Memory, attention and decision process

It is difficult to remember all the many drugs that are affected by kidney function, and that different recommendations apply to different drugs.

"It's remembering which medications you need to be careful with, those are the pitfalls." (P12)

"It's just remembering lots and lots and lots of anomalies isn't it. Different facts about drugs…but you can't apply to any other drug, it's often just applicable to drug you have in mind." (P14)

For drugs that are more regularly prescribed it might be easier to remember to check kidney function.

"I can remember that [nitrofurantoin] *and that's easy, but with other stuff, you know like NSAIDs, or the one that I didn't – pause – was it metformin is the one I don't think about very often, cos I don't regularly prescribe it." (P2)*

"I suppose I just carry nuggets of bits of information around the place - the things that you're using more day to day." (P11)

Triggers to reviewing the kidney function in relation to prescribing expressed were

- Past experience of an adverse drug reaction.

  "Patients who were really ill as a result of drugs they had been given and I think I am more wary." (P8)

- Old age.
  "I'd probably have to think about age. Age would probably be a trigger." (P7)

- Acute reduction in kidney function.
  "…and occasionally you'll see renal changes cos of meds and oh quick change them back and hope things pick up." (P4)

  "If the eGFR was getting worse then I would think of an alternative." (P10)

- Warnings and prompts.
  "GPs are very good at being led by instruction. You know if it says use this, we will do it!" (P6)

- 'Flags' already in the head.
  "The ones in my head that I know are good or bad I will be looking at it – It's the ones that flag up, yes." (P11)

Kidney function was more likely to be thought of when first prescribing a drug.

"I think that's easier to apply [when newly prescribing], have that sort of red flags you know thought processes, let's be careful." (P11)

"When you're starting a new medication you start to pay a bit more attention to them." (P9)

However, kidney function is not thought about at medication review and attention is likely to be on other things that might not be related to the drugs.

"Renal function isn't one of the things that we benchmark against when we review medications." (P12)

"I think it's so QOF orientated now, you know we are focused on perhaps the wrong stuff in medication reviews." (P7)

There are no warnings and prompts when doing a medication review.

"With the medication review you've just got a list of the drugs in front of you – So you've got to have I guess that knowledge either. Well it's got to be in your head or to trigger." (P11)

Warnings and prompts for drug use in RKF are generalised and not patient specific so tend not to be looked at.

"It's so generalised it becomes more easy to maybe not look at it as you should." (P7)

Behavioural regulation

A kidney function test result is needed before the medication review is done, which doesn't tend to happen currently.

"We do the medication review and then we look and say oh yes and you'll need a blood test cos you're on these pills and then they go off and have a blood test and you never then actually look at the medications again in the context of the result." (P12)

"You look at the result and you think oh well that's a stable, slightly low eGFR and nothing to worry about , but you don't really go back and do it the other way and maybe we ought to be trying to do bloods before med reviews." (P12)

Improved computer decision support was seen as something that could help.

"I need a button to just say to check on to highlight all drugs that are a problem or whichever GFR or if it could do that to their repeat list for you." (P15)

"SystmOne, SystmOne. Please flash up do not use eGFR, you must use creatinine clearance for this." (P6)

It was expressed that there was a habit of prescribing the dose of a drug that they just always use without thinking that it might need altering.

"Nitrofurantoin – again just 100bd – I use a lot in the elderly so I have to hold my hands up." (P4)

Examples mentioned that have changed participant practice were reading up and learning about a specific drug, pharmacist teaching, and computer alerts.

Physical capability

Table 41 was developed to chart the themes in the one domain for physical capability: Skills. The skills domain had themes from 13 of the interviewees, but was one of the more minor domains in terms of number of times themes were discussed.

Skills

Kidney function is often checked, but the result is not then assessed in relation to prescribing and review of medications.

"We often check the bloods when we do a medication review that haven't done - I don't often drill, ever is probably the right word, drill down to the eGFR to see whether any of the medications that they're on tally with the GFR." (P9)

"We are very good at knowing when to re-check the U&Es, but are we actually correlating that with what people are on?" (P7)

Most of the GPs did not know what to do or how to calculate CrCl, but those that knew how to use the SystmOne renal calculator didn't think it was difficult.

"I wouldn't know how to calculate it." (P7)

"You can go into the clinical tools thing, can't you, to create it or calculate it– I don't think that bit's difficult." (P12)

The process within prescribing was expressed as complex, multi-stage and difficult.

"I think it is difficult; I think it just a lot of steps isn't it?" (P5)

"When prescribing decisions start to get complicated and difficult and it's after about 4 or 5 drugs then you're really into uncharted territory sometimes with unpredictable outcomes." (P14)

		length of prescribing experience			GP trainer Y/N	knew me/ heard me			Skills domain							
Participant	M/F	<8yrs = 1	8-18yrs = 2	>18yrs = 3		NN	YN	YY	skills	Understanding leads to remembering and ability to apply	Difficult to do	Checking kidney function	U&Es checked but not related to drugs	Calculation of kidney function estimate	Relating kidney function estimate to drugs	number of different knowledge themes mentioned per participant
P1	M		2		Y		YN		✓			✓			✓	2
P2	F	1			N	NN			✓	✓						1
P4	M		2		Y	NN			✓	✓						1
P5	F		2		N		YN		✓		✓					1
P6	F		2		Y		YN									0
P7	F		2		N		YN		✓				✓	✓		2
P8	M			3	Y			YY	✓						✓	1
P9	M		2		Y			YY	✓		✓		✓	✓		3
P10	F		2		Y		YN		✓		✓					1
P11	F		2		N			YY	✓		✓			✓	✓	3
P12	F			3	Y			YY	✓			✓		✓		2
P13	F		2		N			YY	✓			✓				1
P14	M			3	Y		YN		✓		✓			✓		2
P15	F	1			N	NN			✓	✓	✓					2
Number of participants mentioning the theme									13	3	6	3	2	5	3	22

Abbreviations: M/F: male/ female; Y/N: yes/ no.

Table 41: Physical capability: charting themes in 1 TDF domain

4.5.4.3   What needs to change for more opportunity?

Figure 31 shows the barriers and enablers for what needs to change for greater opportunity.

Physical opportunity

Table 42 shows the table developed to chart the themes in the domain for physical opportunity: environmental context and resources.

Opportunity

Physical opportunity	Social opportunity

Enablers

Resources as facilitators: BNF PSS materials pharmacist advice on-line information phone app	
	a good role model is a facilitator
	pharmacist influence

Environmental context & resources	Social influences

Barriers

if don't have a kidney function estimate then cannot apply the recommendations	belief that if other GPs aren't doing it in practice then that is how they will be judged and so would continue as are doing
many steps to prescribing	
takes time	not discussed amongst colleagues
behaviour is rushed; squeezed at the end of a consultation	
lack of time	
competing priorities	
aging population	
reporting of eGFR when need CrCl	
no computer decision support on a home visit	

Abbreviations: BNF: British National Formulary; CrCl: creatinine clearance; eGFR: estimated glomerular filtration rate; PSS: Prescribing Support Services (pharmacy team).

Figure 31: Perceptions of barriers and enablers for what needs to change for more opportunity.

Participant	M/F	Length of prescribing experience (1=<8yrs, 2=8-18yrs, 3=>18yrs)	GP trainer Y/N	knew me/ heard me (NN/YN/YY)	Environmental context and resources	Competing priorities and time constraints	Time taken related to the behaviour	Prescribing squeezed at end of consultation	Time constraints	Competing priorities	Workload/ number of patient/ aging population	Uses the BNF	PSS materials	Pharmacist advice	On-line information	Phone app	Equations – using eGFR	Path lab reporting – don't do CrCl	Don't have if away from the computer e.g. home visit	Computer resource useful and used	Don't have warnings at medication review	Problems with the computer system	Warning stars	Problem of CKD coding	Inconsistencies in resources	What wanted from computer system	number of different knowledge themes mentioned per participant
					Environmental context and resources domain																						
P1	M	2	Y	YN	✓	✓		✓		✓				✓													3
P2	F	1	N	NN	✓	✓				✓										✓					✓		4
P4	M	2	Y	NN	✓	✓			✓			✓					✓	✓			✓				✓		6
P5	F	2	N	YN	✓	✓	✓			✓						✓				✓		✓					5
P6	F	2	Y	YN	✓	✓				✓		✓		✓	✓		✓			✓							5
P7	F	2	N	YN	✓							✓					✓					✓					3
P8	M	3	Y	YY	✓	✓					✓														✓	✓	4
P9	M	2	Y	YY	✓	✓	✓		✓														✓				3
P10	F	2	Y	YN	✓	✓			✓	✓								✓									4
P11	F	2	N	YY	✓	✓				✓		✓	✓							✓		✓				✓	6
P12	F	3	Y	YY	✓	✓			✓			✓	✓	✓				✓	✓	✓							7
P13	F	2	N	YY	✓	✓	✓		✓		✓	✓		✓			✓			✓	✓	✓	✓	✓			9
P14	M	3	Y	YN	✓	✓	✓		✓			✓		✓						✓	✓	✓				✓	7
P15	F	1	N	NN	✓																	✓	✓				3
Number of participants mentioning the theme					14	12	4	1	6	6	2	7	2	5	1	1	4	3	1	7	3	6	3	1	3	3	69

Abbreviations: CKD: chronic kidney disease; CrCl: creatinine clearance; eGFR: estimated glomerular filtration rate; M/F: male/ female; Y/N: yes/ no; PSS: Prescribing Support Services (pharmacy team).

Abbreviations: BNF: British National Formulary; CKD: chronic kidney disease; CrCl: creatinine clearance; eGFR: estimated glomerular filtration rate; M/F: male/ female; Y/N: yes/ no; PSS: Prescribing Support Services (pharmacy team).

Table 42: Physical opportunity: charting themes in 1TDF domain

The environmental context and resources domain had the greatest number of different themes identified, which were the most discussed, and by all participants.

Environmental context and resources

Time constraints and prescribing being squeezed at the end of a consultation were frequently expressed as making it difficult to think about kidney function when prescribing.

> *"To then go out and see exactly what their eGFR is and then the exact recommendations for that drug and all of that's very time consuming." (P5)*

> *"Prescriptions are done at the end and consultations often run over and the GP might be rushed and perhaps don't do it as well as they should do." (P1)*

Competing priorities and information overload were also mentioned by many participants.

> *"I think we're just awash with information really and it's sometimes hard to know how to prioritise some time." (P14)*

> *"The reality is that the world we live in in general practice is there are lots of boxes to tick – have you checked the blood pressure, have you done the BMI, code this, code that, do that.," (P1)*

Reporting eGFR with the pathology lab reports means it is easily accessible and so is more likely to be used than CrCl.

> *"eGFR being on the bottom of the bloods is fab, cos it means everyone that's had a U&E has got their eGFR so you'd check that…That becomes a problem, doesn't it, because everything is based on eGFR. All your QOF data is based on eGFR." (P4)*

Resources are used, with the British National Formulary (BNF, 2015), on-line information, medicines management team documents, pharmacists and a phone-app being mentioned. The BNF was a key resource but the front section on 'prescribing in renal impairment' was not known about, and the advice on the different kidney function equations was unclear.

> *"I was just looking at what the BNF said about the rivaroxaban...cos I wanted to know whether it talks about creatinine clearance, no it doesn't , it talks about eGFR - following the BNF would give her too much rivaroxaban." (P4)* [note, the BNF has since been altered to state that CrCl should be used]

Home visits were raised as an issue, and having the information available.

> *"I suppose you have to be at a PC, cos it's difficult to be done on a home visit." (P11)*

Participant	M/F	length of prescribing experience			GP trainer Y/N	knew me/ heard me			Social influences domain						
		<8yrs = 1	8-18yrs = 2	>18yrs = 3		NN	YN	YY	Social influences	Influence of trusted colleague	Pharmacist influence	Comparison with other GPs	GP more than hospital doctors	Not generally discussed with colleagues	number of different knowledge themes mentioned per participant
P1	M		2		Y		YN		✓		✓				1
P2	F		1		N	NN			✓			✓			1
P4	M		2		Y	NN									0
P5	F		2		N		YN								0
P6	F		2		Y		YN								0
P7	F		2		N		YN		✓				✓		1
P8	M		3		Y			YY	✓			✓			1
P9	M		2		Y			YY	✓		✓				1
P10	F		2		Y		YN								0
P11	F		2		N			YY	✓		✓				1
P12	F		3		Y			YY	✓					✓	1
P13	F		2		N			YY	✓					✓	1
P14	M		3		Y		YN		✓	✓	✓				2
P15	F		1		N	NN									0
Number of participants mentioning the theme									9	1	4	2	1	2	10

Abbreviations: M/F: male/ female; Y/N: yes/ no.

Table 43: Social opportunity: charting themes in 1 TDF domain

Social opportunity

Table 43 shows the table developed to chart the themes in the domain for social opportunity: social influences.

The social influences domain had the fewest different themes elucidated, and lowest degree of mentions by participants.

Social influences

Kidney function and prescribing was not an area discussed amongst GPs, but it was suggested that perhaps there should be more discussion and sharing of knowledge.

> "*We don't really talk, I can't say that ever I sit round and talk to the others about this. When you're making prescribing decisions you usually make them on your own.*" (P13)

> "*When you share good practice with other people you pick up tips from them… I think there should be more sharing of knowledge… it's very useful to share information this way.*" (P14)

Variability in the prescribing of colleagues was mentioned.

> "*I am sometimes a little surprised at the prescribing of colleagues to elderly patients, for instance using high dose of things like non-steroidals, er, maybe starting ACE inhibitors at higher doses than I would.*" (P8)

> "*I think it's an area of huge variability between practitioners – I have noticed.*" (P15)

Pharmacists were highlighted as having an influence on prescribing.

Motivation

Reflective motivation	Automatic motivation

Enablers

seen as important and relevant

motivation is to prescribe as best as possible

prescribing is a responsibility of GPs

motivation is to not do harm

GPs should be good at prescribing

a GP role is to prescribe safely

bad experience/ crisis make cautious

warnings when needed in the prescribing process (currently at initiation)

prescribing is a responsibility

responsibility at medication review as kidney function might have changed since the last review

incentives to apply

belief that inappropriate prescribing in reduced kidney function can cause harm for patients

computer decision support to prompt and reinforce behaviour

stress/ concern/ worry about not prescribing correctly and causing a patient harm

confidence expressed in diabetes

triggers

Professional role & identity	Belief in capabilities	Motivation & goals	Belief in consequences	Reinforcement	Emotion

Barriers

not feeling reponsibility for the continued prescribing of a drug at medication review (because somone else started it)

a complex behaviour so cannot rely on human function or there are bound to be mistakes

lack of motivation if the patient is 'OK' (BP, QOF etc all normal - no trigger to check)

mistakes will happen because it is

warnings are not flagged at medication review

fear of overload

knowledge makes the job harder

bombardment with screen messages

not motivated to change behaviour if not convinced of importance

warnings are not specific

reponsibility for longer term monitoring rests with other healthcare professionals

less capability at medication review

omission bias - harm from an act of commission feels worse that that of omission

relating to kidney disease when not about CKD but about drug use and dosing

conflicting goals (e.g. nitrofurantoin vs push to use)

Abbreviations: BP: blood pressure; QOF: Quality Outcomes Framework.

Figure 32: Perceptions of barriers and enablers for what needs to change for stronger motivation.

Participant	M/F	length of prescribing experience			GP trainer Y/N	knew me/ heard me			Nature of the behaviour	Prescribing is a responsibility	Too many steps to prescribing	Automatic behaviour	Do at drug initiation but not at drug review	Easier to remember if regularly prescribe	Easy when know how/ can look up/ when logical	Not unreasonable to expect a clinician to look it up	Assessing kidney function using eGFR	For older people start with lower doses	Difficult to do	Behaviour done every day	Time point 1 at initiation of drug	Time point 2 when reviewing/ reauthorizing the drug	Make simple	Teach medical students the theory	Computer system to prompt behaviour	Do KF test before med review	dissemination	number of different knowledge themes mentioned per participant
		<8yrs = 1	8-18yrs = 2	>18yrs = 3		NN	YN	YY	**Nature of the behaviour domain**																			
P1	M		2		Y		YN		✓						✓	✓						✓	✓						4
P2	F	1			N	NN			✓					✓	✓				✓									3
P4	M		2		Y	NN			✓			✓					✓		✓									3
P5	F		2		N		YN		✓		✓													✓					2
P6	F		2		Y		YN		✓								✓						✓		✓	✓		✓	5
P7	F		2		N		YN		✓	✓			✓															2
P8	M			3	Y			YY																					0
P9	M		2		Y			YY																					0
P10	F		2		Y		YN																						0
P11	F		2		N			YY	✓									✓		✓							✓		3
P12	F			3	Y			YY																					0
P13	F		2		N			YY	✓								✓												1
P14	M			3	Y		YN		✓								✓		✓										2
P15	F	1			N	NN																							0
Number of participants mentioning the theme									9	1	1	1	1	1	2	1	4	1	3	1	1	2	1	1	1	1	1	25

Participant	M/F	length of prescribing experience			GP trainer Y/N	knew me/ heard me			Emotion	Difficult to cope with causing harm by error of commission	Stress/bothered/worry if not doing it correctly	Shocked/ frightened at what don't know	Concern/ fear re drugs and RKF	Fear of overload	Worry re BNF	Computer messages eliciting emotion	number of different knowledge themes mentioned per participant
		<8yrs = 1	8-18yrs = 2	>18yrs = 3		NN	YN	YY	**Emotion domain**								
P2	F	1			N	NN			✓		✓						1
P15	F	1			N	NN											0
P4	M		2		Y	NN			✓						✓		1
P5	F		2		N		YN		✓					✓			1
P7	F		2		N		YN		✓		✓						1
P1	M		2		Y		YN		✓					✓			1
P6	F		2		Y		YN		✓				✓				1
P10	F		2		Y		YN										0
P14	M			3	Y		YN										0
P11	F		2		N			YY	✓			✓					1
P13	F		2		N			YY	✓			✓				✓	2
P9	M		2		Y			YY	✓		✓						1
P8	M			3	Y			YY	✓	✓						✓	2
P12	F			3	Y			YY	✓			✓	✓			✓	3
Number of participants mentioning the theme									11	1	3	3	2	2	1	3	15

Abbreviations: BNF: British National Formulary; KF: kidney function; M/F: male/ female; RKF: reduced kidney function; Y/N: yes/ no.

Table 44: Automatic motivation: charting themes in 2 TDF domains

4.5.4.4 What needs to change for stronger motivation?

Figure 32 shows the barriers and enablers found on what needs to change for stronger motivation.

Automatic motivation

Table 44 shows the two tables developed to chart the themes in the domains for automatic motivation:

> Nature of the behaviour (presented here, but when the themes were remapped to the updated 14 domain TDF model, some of the themes were 'reinforcement', and others were moved to 'behavioural regulation')
> Emotion

Both these domains had lower numbers of themes found, and were mentioned less than other domains.

Reinforcement

Computer warnings and prompts about reduced kidney function are useful and used.

> "*It does come up when you prescribe doesn't it so it does say be careful in renal impairment and you know the little alert comes up.*" (P13)

> "*It does what it's supposed to do [computer warning] and it makes you stop and check.*" (P12)

However, warnings and prompts do not come up at medication review.

> "*Once they are on the repeats it doesn't then, doesn't then flag it up again.*" (P4)

The warnings and prompts are not patient specific.

> "*Not specific, doesn't tell what to do, pop up boxes and templates often not useful or helpful, too frequent.*" (P3)

> "*I don't use that [screen that pops up] as, as it's a warning, but it doesn't tell me what to do.*" (P14)

Some expressed that they only notice warnings with '3 stars' i.e. a major warning.

> "*Often there is so much information in there, but unless it's got three stars next to it you don't actually pay that much attention to it for every prescription, which is bad, but you don't!*" (P13)

Emotion

The emotions expressed were particularly about the stress and worry around prescribing and causing harm when getting it wrong.

"We are still diagnosing and prescribing as our primary function, you know if we are not getting that function right that bothers me really." (P9)

"It becomes stressful when you're informed about something and so my prescribing could be doing patients harm, but I don't have enough knowledge to change my prescribing." (P2)

Errors which occur as a result of an action by the prescriber were seen as particularly difficult to deal with emotionally.

"Errors of commission are almost impossible to cope with because you have done something to that patient that's harmed them. That's the problem with renal function." (P8)

One participant was shocked that they hadn't known about drugs they used regularly being affected by kidney function.

"I was really shocked that I didn't know about gabapentin, as I think I am fairly on the ball." (P6)

Fear was expressed about renal medicine.

"I think the students are still terrified about renal medicine. I think it's quite a difficult area of medicine." (P11)

"It's just a minefield I think." (P12)

Reflective motivation

Table 45 shows the four tables developed to chart the themes in the domains for reflective motivation:

> Professional role and identity
>
> Motivation (intentions) and goals
>
> Beliefs in capabilities and optimism
>
> Beliefs about consequences

The 'beliefs about consequences' domain had themes from all interviewees, and 'beliefs in capabilities and optimism' from all but one. 'Beliefs about consequences' and 'motivation (intentions) and goals' both had high numbers of themes discussed across the participants.

Social/ professional role and identity domain

Participant	M/F	<8yrs = 1	8-18yrs = 2	>18yrs = 3	GP trainer Y/N	NN	YN	YY	Social/ professional role and identity	GP role	GPs should be good at prescribing	Important role to think about toxicity/ safety	GP can be pragmatic with information	Peer discussion	Feel less responsible if started by another prescriber	Reviewing is more a role for another HCP	number of different knowledge themes mentioned per participant
P1	M		2		Y		YN		✓	✓		✓				✓	2
P2	F	1			N	NN											0
P4	M		2		Y	NN			✓	✓				✓			1
P5	F		2		N		YN		✓	✓				✓			1
P6	F		2		Y		YN		✓	✓			✓				1
P7	F		2		N		YN		✓					✓			1
P8	M			3	Y			YY									0
P9	M		2		Y			YY	✓	✓	✓	✓					2
P10	F		2		Y		YN		✓							✓	1
P11	F		2		N			YY									0
P12	F			3	Y			YY									0
P13	F		2		N			YY	✓	✓	✓						1
P14	M			3	Y		YN										0
P15	F	1			N	NN			✓	✓					✓		1
Number of participants mentioning the theme									9	7	2	2	1	3	1	2	11

Motivation and goals domain

Participant	M/F	<8yrs = 1	8-18yrs = 2	>18yrs = 3	GP trainer Y/N	NN	YN	YY	Motivation and goals	Important	Relevant	Motivation is not doing harm	Important in older people	• Bad experience makes cautious	incentive as motivation	holistic care as motivation	motivation is to prescribe as best as possible	not motivated if patient is OK	not motivated without being convinced of importance	number of different knowledge themes mentioned per participant
P1	M		2		Y		YN		✓			✓			✓		✓			3
P2	F	1			N	NN			✓										✓	1
P4	M		2		Y	NN			✓	✓	✓	✓						✓		4
P5	F		2		N		YN		✓				✓	✓						2
P6	F		2		Y		YN		✓			✓								1
P7	F		2		N		YN		✓	✓		✓								2
P8	M			3	Y			YY	✓	✓		✓		✓						3
P9	M		2		Y			YY	✓	✓										1
P10	F		2		Y		YN		✓	✓			✓		✓					3
P11	F		2		N			YY	✓	✓		✓								2
P12	F			3	Y			YY	✓			✓				✓				2
P13	F		2		N			YY	✓	✓			✓							2
P14	M			3	Y		YN													0
P15	F	1			N	NN			✓		✓									1
Number of participants mentioning the theme									13	7	2	7	3	2	2	1	1	1	1	27

Beliefs about capabilities domain

Participant	M/F	<8yrs = 1	8-18yrs = 2	>18yrs = 3	GP trainer Y/N	NN	YN	YY	Beliefs about capabilities	done badly	lack of confidence in capability	lack of confidence without computer support	confidence in capability in diabetes	do-able	number of different knowledge themes mentioned per participant
P1	M		2		Y		YN		✓		✓	✓			2
P2	F	1			N	NN			✓		✓				1
P4	M		2		Y	NN			✓		✓				1
P5	F		2		N		YN								0
P6	F		2		Y		YN		✓					✓	1
P7	F		2		N		YN		✓		✓				1
P8	M			3	Y			YY	✓				✓		1
P9	M		2		Y			YY	✓		✓				1
P10	F		2		Y		YN		✓				✓		1
P11	F		2		N			YY	✓				✓		1
P12	F			3	Y			YY	✓		✓				1
P13	F		2		N			YY	✓	✓	✓				2
P14	M			3	Y		YN		✓	✓	✓				2
P15	F	1			N	NN			✓		✓				1
Number of participants mentioning the theme									13	2	9	1	3	1	16

Participant	M/F	length of prescribing experience <8yrs = 1	8-18yrs = 2	>18yrs = 3	GP trainer Y/N	knew me/ heard me NN	YN	YY	Beliefs about consequences	Drug use in RKF can cause harm	Drug doesn't work	Drug can cause toxicity to kidney	Can cause toxicity from the drug	Can cause significant harm/ hospitalisation	Knowledge makes it difficult	Complexity make it unsafe	Kidney function affects drugs	Prescribing errors common	Unintended knock-on effect	number of different knowledge themes mentioned per participant
									Beliefs about consequences domain											
P1	M		2		Y		YN		✓	✓			✓			✓				2
P2	F	1			N	NN			✓	✓	✓								✓	2
P4	M		2		Y	NN			✓	✓		✓				✓		✓		3
P5	F		2		N		YN		✓	✓				✓				✓		2
P6	F		2		Y		YN		✓	✓			✓							1
P7	F		2		N		YN		✓	✓			✓			✓	✓			3
P8	M			3	Y			YY	✓	✓	✓		✓	✓			✓			4
P9	M		2		Y			YY	✓	✓			✓							1
P10	F		2		Y		YN		✓	✓		✓					✓			2
P11	F		2		N			YY	✓	✓		✓					✓			2
P12	F			3	Y			YY	✓	✓	✓	✓	✓							3
P13	F		2		N			YY	✓	✓	✓	✓	✓		✓					4
P14	M			3	Y		YN		✓	✓		✓		✓			✓	✓		4
P15	F	1			N	NN			✓						✓					1
Number of participants mentioning the theme									14	13	4	6	7	3	2	3	5	3	1	34

Abbreviations: HCP: healthcare professional; M/F: male/ female; RKF: reduced kidney function; Y/N: yes/ no.

Table 45: Reflective motivation: charting themes in 4 TDF domains

Social/ professional role and identity

Prescribing in general was expressed as a responsibility and that it is a GP role to be 'good' at it.

> "*I still find it a responsibility when you're prescribing something.*" (P7)

> "*I do think it's important for GPs to be top of the ladder in prescribing because it's mainly our primary function.*" (P9)

It is a GP role to think about toxicity and safety and that they should look it up if needed.

> "*Toxicity is important, it is probably one of the biggest things a GP will think of I would think.*" (P6).

> "*I don't think that is unreasonable to do and to check and to expect a clinician to look that up.*" (P1)

However, less responsibility was felt when doing a medication review and that longer-term monitoring might be something that was done by another healthcare professional.

> "*When you are continuing something that somebody else has started, this is wrong probably, but you feel less a responsible decision to continue something. That's wrong I admit.*" (P7)

> "*If we are talking about longer term monitoring, I suppose that falls into the area of what people like yourself and* [Y] *do isn't it.*" (P1)

Motivation (intentions) and goals

To apply the recommendations for prescribing in RKF was seen as important and relevant.

"It feels important, it feels important, and it feels like something that the more I get reminded of it the more important." (P9)

"Oh, it's very relevant." (P4)

Not doing harm to patients is a prime motivation.

"We want people to tolerate medications that we are giving them, we want to reduce side effects, we want to improve compliance, we don't want to basically cause anyone any harm, so yes it's very important." (P7)

"I suppose everybody follows the rule first do no harm." (P8)

Previous bad experiences add caution in prescribing.

"When you've had a few bad experiences over the years you're extra cautious aren't you?" (P8)

However, it was also brought up that if a patient appears stable then they are less likely to check parameters such as kidney function.

"I am checking they're still ok, blood pressure still ok, QOF data is alright, must be fine and they feel they are ok so it must be fine let's move them on." (P4)

Understanding leads to remembering and ability to apply.

"I need to understand why because of that I need to understand why I can't prescribe it. I need to know that, partly to help me remember and also that knowing it would affect how I prescribe it." (P15)

Reduced kidney function as an area is neglected, ignored or something that is given little attention or care.

"It's a 'Cinderella' area isn't it I suppose." (P12)

Beliefs in capabilities and optimism

The majority of comments made were that the GPs were not confident in their capabilities; the one exception was for those with an expertise in diabetes.

"We tend to do them [medication reviews] very badly and sort of rush through them, so I have to say I don't really do it properly. I should do!" (P14)

"I am not prescribing as safely as I could be in regards to these areas." (P9)

There was a lack of confidence in prescribing without computer support.

"It is so complex as is medicine, increasingly complex to that to rely on human, to rely on human functions to pick up everything, there is bound to be mistakes." (P1)

It was felt there was more capability at drug initiation than at medication review.

"I'm probably quite good about thinking about kidney function when I'm starting new medications, but probably not very good when I'm reviewing them." (P7)

Beliefs about consequences

There was an understanding that drug use in RKF can cause harm to patients from toxicity to the kidneys, increased risk of adverse drug reactions, hospitalisation, and drugs being ineffective.

"The reasons why these drugs have indications that their dose should be adjusted, or avoided, at a certain renal function is because it's harmful and of course what we are doing is not doing harm isn't it." (P1)

"I did have a patient that did have a low eGFR and prescribed her nitrofurantoin and then she ended up in hospital as a result of it really. So that was a learning point for me." (P5)

Consequences on the prescribing process were expressed that increased knowledge makes the reviews harder as there is more to assess. Also that there needs to be good communication in the prescribing decision to make actions clear in the record.

"Knowledge! Cos if you don't know something then you're not going to pick it up are you. So medication reviews would be really easy if you didn't know anything." (P13)

"If I'm seeing a patient again or someone else is seeing them to be able to look back and work out why they have been given this random drug dose, because if another doctor calculates the creatinine clearance, you know, otherwise where is the transparency?" (P2)

4.5.4.5 Differences with participant type

Themes were generally spread over all respondent types and there were very few patterns found when analysing the data by participant type.

An exception was that the four participants with over 18 years' prescribing experience did not express a lack of knowledge, or any themes to do with social and professional role. However, it was this group that said medication reviews are done badly, and that they were shocked at what they don't know.

The participants with less than 8 years' experience added no themes in the 'memory, attention and decision-making' domain.

Only GP trainers mentioned that is an important GP role to think about toxicity and safety.

For those that knew me and had experienced a workshop and audits on prescribing in reduced kidney function said that it is easier to remember if they do it more often and were more likely to have skills and knowledge, but some still said it was difficult to do.

4.5.4.6   The key themes identified on what needs to change

The 'key themes' resulted from a synthesis of the range of themes elucidated, noting where themes were frequently mentioned, but also where there might be high importance for an intervention, even if only mentioned by one interviewee.

As previously highlighted, themes were found across all the TDF domains, with at least 9 of the interviewees discussing issues in every domain. Themes on 'knowledge', 'environment and resources', and 'beliefs about consequences' were mentioned by all 14 interviewees recorded implying that these are important to all the wide range of GPs included. The domains with the greatest number of themes from the interviewees were environment and resources, knowledge, memory, attention and decision process, beliefs about consequences, and motivation and goals. One participant raised that they felt less responsibility when doing a medication review for a drug started by someone else, and another suggested that longer-term monitoring might be something that was done by another healthcare professional. These themes were mentioned only once but were considered important when developing the key themes.

The resulting six key themes are listed below with exemplar quotes:

Key theme 1: in primary care there is a lack of awareness, knowledge, and understanding about prescribing in the reduced kidney function of older people.

> *"I suspect for some clinicians, and I include myself in that, there may be a knowledge gap." (P1)*

> *"I wasn't aware. This is terrible because I use a lot of gabapentin and pregabalin, obviously, in neurology." (P6)*

Key theme 2: kidney function testing is required and needs assessment when prescribing.

> *"We often check the bloods…but I don't often drill, ever is probably the right word, drill down to the eGFR to see whether any of the medications that they're on tally with the GFR." (P9)*

> *"We are very good at knowing when to re-check the U&Es, but are we actually correlating that with what people are on?" (P7)*

Key theme 3: the application of kidney function level to prescribing decisions is needed at both drug initiation and at medication review.

"Renal function isn't one of the things that we benchmark against when we review medications." (P12)

"When you are continuing something that somebody else has started, this is wrong probably, but you feel less a responsible decision to continue something. That's wrong I admit." (P7)

Key theme 4: there is difficulty in remembering to apply the recommendations for use, and dosing, of drugs in reduced kidney function.

"It's remembering which medications you need to be careful with, those are the pitfalls." (P12)

"I think it's so QOF orientated now, you know we are focused on perhaps the wrong stuff in medication reviews." (P7)

Key theme 5: there is a need to embed kidney function assessment within the prescribing process.

"It [prescribing] is so complex, as is medicine, increasingly complex, so that to rely on human functions to pick up everything, there are bound to be mistakes." (P1)

"I need a button to just…check on to highlight all drugs that are a problem." (P15)

Key theme 6: there is limited use and confusion with the resources available to support the use, and dosing, of drugs in reduced kidney function.

"I was just looking at what the BNF said about the rivaroxaban...cos I wanted to know whether it talks about creatinine clearance, no it doesn't , it talks about eGFR - following the BNF would give her too much rivaroxaban." (P4) [Note: the BNF has now altered the recommendations for NOACs to be CrCl, but not for any other drugs]

"I should read that [looking at the BNF section on prescribing in renal impairment].*" (P2)*

4.6 Discussion

4.6.1 Principal findings

GPs need awareness, education and support to apply the prescribing recommendations in reduced kidney function (RKF). There is a need to raise

awareness and provide education on prescribing in RKF for all prescribers and specialities, and assessing kidney function needs to be made easier in the prescribing process. Patient and drug specific warnings and prompts are needed at medication review as well as initiation.

Summary of what needs to change for greater capability

There was a lack of awareness and knowledge for all levels of experience so increasing awareness and education is needed for all prescribers, and in clinical specialities, on prescribing renally excreted drugs.

Although GPs checked kidney function it was not always thought of when prescribing, and particularly not at medication review. A kidney function test should be done before medication review so that it can be assessed whether drug choice and dosing is still appropriate.

Most GPs did not know of the creatinine clearance calculation or how to do it. The skill is easy when it is known what to do, but the process is difficult as it is complex, multi-step, and not part of the prescribing process.

Summary of what needs to change for more opportunity

Competing priorities, workload and time constraints make it difficult to assess kidney function when prescribing so it needs to be made easier in the care pathway and given greater priority to reduce risk of harm.

Kidney function estimation using creatinine clearance estimated using the Cockcroft & Gault equation needs to be made easier in the prescribing process.

Resources are used, mainly the BNF, but others were mentioned that could be helpful if known about more widely, such as on-line information and phone apps. However, the BNF information needs clarifying as the front section on 'prescribing in renal impairment' was not known about and the advice on eGFR versus CrCl is confusing. Guidelines could be improved to include advice on use of the relevant drugs when kidney function is low.

Summary of what needs to change to strengthen motivation

GPs see prescribing safely as an important role and there was an understanding that harm can be caused by drugs when kidney function is low, but they were not confident in their abilities to apply the recommendations for prescribing in RKF.

Not having warnings and prompts at medication review was a particular barrier, and there was less of a sense of responsibility expressed for prescribing at this point in the care pathway. Patient and drug specific warnings and prompts at both drug initiation

and at medication review would be useful as a reminder when kidney function needs to be taken into consideration.

4.6.1.1 Prescribing behaviour in primary care

Bradley, in 1992, qualitatively sought to understand how prescribing decisions are made in primary care and exposed the complexity of decision-making that precedes prescribing. He highlighted discomfort with prescribing and the struggle to balance several disparate considerations; also that ignorance was a factor but that it is often other things that have more impact such as negotiating change in treatment. This echoes findings in the current study and if prescribers have been unaware of kidney function when prescribing, it will add another level of complexity.

Since the 1990s most focus has still been in hospitals with less attention to major sources of harm in primary care, such as prescribing (Guthrie et al, 2011). The only paper found purporting to 'assess GP prescribing behaviour for elderly patients with renal failure' was a short report from France (Jonville-Béra et al, 2008); they used a questionnaire study to find that GPs do not sufficiently consider renal function of elderly patients and showed a lack of knowledge, but they did not explore why.

The finding that there was less responsibility felt for prescribing at medication review was similar to a recent study by Slight et al (2013) where there was acknowledgement by some GPs that they became 'slightly blasé' about the treatment of patients they had known for a long time. They suggested that there may be benefits to using practice pharmacists to review repeat medications (Avery et al, 2012).

Understanding the factors related to prescribers in stopping or altering a medication they have been on for some time had been explored in a recent systematic review (Anderson et al, 2014). Again, many factors were found to be involved which were highly interdependent and impacted by considerable clinical complexity. In polypharmacy, prescribers could not easily identify which medications were inappropriate; they state that the finding of prescribers being unaware is not surprising as they do not intentionally prescribe inappropriately. This was mentioned in the GP interview study. The prescribers rationalised continuation with the belief that the drugs work and have few adverse effects; they identified different thresholds for initiation versus continuation of a drug which suggested lack of prescriber insight.

The Anderson et al study (2014) also discussed 'inertia' as in failure to 'deprescribe' when appropriate. Inertia has been linked to 'omission bias' where harm from an act of commission is felt to be worse than that from an act of omission (Ritov and Baron, 1992; Spranca et al, 1991). This was raised as an issue by one of the participants in

the GP interview study that the perceived potential harm caused if a drug was stopped or a dose reduced because of a low kidney function would be deemed more the fault of the prescriber than would harm from not changing the drug or dose.

4.6.1.2 Reducing prescribing errors

Studies in hospital (Dornan et al, 2009; Dean et al, 2002; Tully et al, 2009; Lawton et al, 2012) have reported similar prescribing 'error-producing conditions' such as lack of training or experience and systems related factors.

The recent qualitative study into the causes of prescribing errors in English general practices (Slight et al, 2013) has highlighted the complex underlying causes within seven categories of high level error-producing conditions: the prescriber, the patient, the team, the working environment, the task, the computer system, and the primary-secondary care interface. Some of the error-producing conditions they found were similar to those found for prescribing for older people with RKF and the results of this GP interview study, such as the prescriber's therapeutic training, drug knowledge and experience, their perception of risk, and the working environment, extensive workload, time pressures, and interruptions. The authors too highlighted the computer-related issues of unnecessary or inappropriate alerts. The current GP interview study has added to these findings by highlighting the problem of having no warnings or prompts at medication review, and the need for them to be patient and drug specific, which would improve medicines safety for other parameters, not just kidney function.

4.6.1.3 The effect of eGFR reporting on prescribing

Quartarolo et al (2007) found that although reporting of eGFR was associated with improved physician recognition of chronic kidney disease in elderly hospitalised patients in California, it did not lead to a change in physician prescribing. Van Pottelbergh et al (2014) also reported that automatic reporting of eGFR did not alter inappropriate prescribing for older people with RKF in Belgium. GPs in this study checked kidney function and had an eGFR available but did not apply it to their prescribing. Ingrasciotta et al (2014) retrospectively looked at use of nephrotoxic drugs before and after diagnosis of CKD and found no change in prescribing.

4.6.2 The key domains and themes

The sample for this qualitative study was recruited to give a wide range of GP expertise and experience, rather than to be representative of all GPs. The aim for the identification of the key themes was therefore not a quantitative analysis of the themes most raised by the interviewees, but an identification of the range of potentially influential determinants.

The analysis of themes, and the identification of domains where many themes have been elucidated, adds an insight into what has been discussed by many of the interviewees, and what might be important across the experience and expertise represented. However, a theme that might be only mentioned by one participant can be an important insight. For example, where one participant revealed that they felt less responsibility for the prescribing at a medication review where the drug had been started by somebody else. When this finding has been presented where GPs are in attendance, including the consensus panel meeting (Chapter 5), this has been recognised in the behaviour of other GPs. Identification of this is likely to be important if an intervention is to be effective.

As previously highlighted, themes were found across all the TDF domains, with at least 9 of the interviewees discussing issues in every domain, which suggests that development of an intervention will need to address a range of determinants. Themes on 'knowledge', 'environment and resources', and 'beliefs about consequences' were mentioned by all 14 interviewees recorded implying that these are important to all the wide range of GPs included. The domains with the greatest number of themes from the interviewees were:

- Environment and resources
- Knowledge
- Memory, attention and decision process
- Beliefs about consequences
- Motivation and goals

These domains are linked to all three COM-B categories suggesting a need for greater capability, more opportunity, and strengthened motivation. Identifying these domains is useful to direct an intervention to where the most barriers or enablers are, and be reflected in the key themes identified.

The synthesis of themes across the COM-B components has resulted in six key themes that give the range of important requirements for change to help prescribers apply recommendations in RKF. It also enabled the future research analysis to determine the prioritisation for intervention (Chapter 5).

4.6.3 Behaviour change wheel (BCW)

The BCW has been developed as a method for characterising and designing behaviour change interventions, synthesising frameworks of behaviour change found in the research literature (Michie et al, 2011).
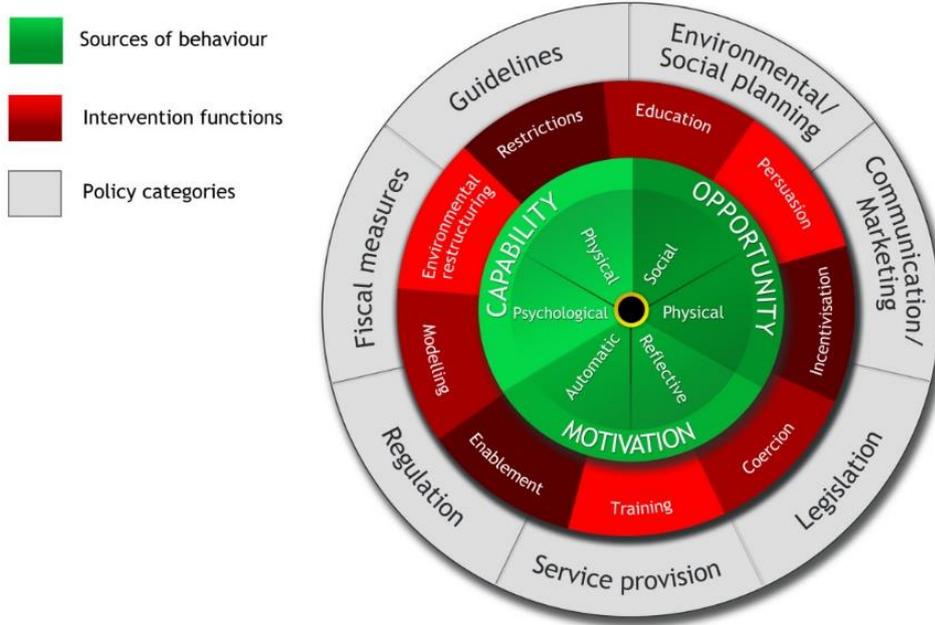
Figure 33: The Behaviour Change Wheel with intervention functions and policy categories (Michie et al, 2011).

Figure 33 shows the wheel with the COM-B model at the core. The BCW also identifies different intervention options that can be applied to changing each of the components, and policies that can be adopted to deliver those intervention functions (Michie et al, 2014). Intervention options in the BCW are described in general terms, such as education, enablement, and environmental restructuring. The policy categories include guidelines and environmental/ social planning.

In this study the TDF has been used to give a more detailed understanding of the behaviour within the COM-B components (Michie et al, 2014, pp 91-93). Linking to COM-B categories will then allow use of the Behaviour Change Wheel for intervention development, identification of relevant behaviour change techniques, intervention functions and policy categories (Michie et al, 2014).

This study has identified key themes that could inform an intervention to encompass greater capability, more opportunity, and strengthen motivation for GP prescribers. However, there is not yet inclusion of the views, opinions and experience of experts, stakeholders and policymakers that could confirm the study findings, and indicate the feasibility and acceptability of the different intervention functions and policy categories. This was addressed in the next study in this programme of research (Chapter 5).

4.6.4 Engagement in the research

Nearly 30% of GPs invited agreed to take part in the qualitative interviews which implied that those who participated were interested and that prescribing safety is a concern to them. However, it did mean that 70% of possible participants did not respond meaning the findings were only from a minority of self-selected GPs. Using the local practice pharmacist team worked well to gain access and deliver recruitment packs. Providing a 'certificate of attendance' (Appendix 10, 8.9) was well received as GPs need evidence of taking part in research for their continuing professional development (CPD).

Guest et al (2006) concluded that about 12 is a sufficient sample for interview studies analysed for emergent themes. In this study no new themes were elicited after 12 participants so fits with the Guest findings; however, it would not have been clear whether, or where, saturation had been reached, and in this study further recruitment was required for the inclusion criteria.

4.6.5 Strengths and limitations

The use of the Theoretical Domains Framework allowed an exploration of the behaviour to give a comprehensive picture of what needs to change. As a non-psychologist with no prior knowledge of behaviour theories, it was extremely helpful to have a framework to systematically explore behaviour in healthcare. An example of the benefit of using a systematic process to understand the issues underlying the behaviour was the important finding that warnings and prompts are not flagged at medication review which had not been recognised as a factor prior to the study. If, for example, the Theory of Planned Behaviour had been used (Ajzen, 1991), the important factors of the habit of always prescribing a dose, the emotion expressed about prescribing, and the many working environment issues might not have been brought out.

Working in primary care helped with gaining access for the study and being able to have participant recruitment packs delivered to GP practice pigeon holes may have helped with recruitment. Prior knowledge of the GP CPD requirements led to the inclusion of a certificate of attendance (Appendix 10, 8.9) being offered which was well received and taken up by all participants.

The effect of myself on the research may reduce the replicability of this study which started from a problem recognised in practice, and so there was professional as well as a researcher involvement in the process, setting, context, and culture (Altheide and Johnson, 1994). Only one researcher conducted the GP interviews and so a

researcher effect is likely to have been consistent across all the interviews. Chew-Graham et al (2002) found that if the researcher was a recognised healthcare professional there were richer and more intuitive responses, and the interviewees were more likely to confide. Certainly rich data was collected. The disclosure of participants that they felt less of a responsibility for the prescribing decision at medication review was an example of the GPs feeling able to confide in something they expressed as being wrong. This also raised the issue of disclosure of negligent practice. Discussion with supervisors led to agreement that this was not an individual disclosure but a theme that would need addressing in an intervention.

It was made clear to participants that the research was being done by a pharmacist working in Bradford primary care. Hoddinott and Pill (1997; 1999) found that her interviewing skills were better if she declared that she was a GP and so concluded that she would always make her professional background clear to respondents. Richards and Emslie (2000) stated that the 'clinical' interviewer should also take care to explain their current role as a researcher.

Chew-Graham et al (2002) also state that there is a risk of shared conceptual blindness and there may have been an assumed shared language and understanding. Doing reflective notes immediately after each interview, and analysis of the dialogue on the transcripts, were used to reflect on myself as the researcher. Analysis of the themes by respondents who knew me previously and those who did not, only showed a difference in skills and knowledge suggesting that the degree to which I was known made little difference to the responses not linked to learning.

The GPs recruited had a wide range of experience and interests and all spoke openly and candidly about their experiences. Data saturation analysis suggested a broad range of the factors influencing prescribing in RKF were recognised.

However, this was a small sample of GPs from the Bradford area thereby limiting external validity. The GPs agreeing to take part were likely to be those more interested in prescribing and more open to scrutiny and so may not be a representative cross-section. Only GPs were included in the sample as the majority of prescribers in primary care; however, there are also non-medical nurse and pharmacist prescribers and they would need to be included in any further research. These data represent the accounts of GPs and might not necessarily accord with their behaviour (Robson, 2011).

4.6.6 What this study adds to the literature

This study has explored GP behaviour when prescribing for older people with RKF. The scoping literature review (Chapter 2) did not find any other research to answer the question of why prescribing recommendations are not applied and so this study has added to the evidence base. The findings have contributed to evidence on prescribing behaviour in primary care, reducing prescribing errors, the lack of effect of eGFR reporting on prescribing, and use of the TDF.

The scoping review also found a lack of theoretical underpinning in the studies aiming to improve prescribing in RKF (Chapter 2, 2.6). This study has sought to explore the determinants that will inform future intervention research.

4.6.6.1 Use of the theoretical domains framework (TDF)

This study adds to the evidence base for the use of the TDF to identify factors influencing the gap between evidence based practice and the routine delivery of health care. Data was found for all domains, including important factors of habit, emotion and the working environment that might not have been elucidated if, for example, the Theory of Planned Behaviour (Ajzen, 1991) had been used. The TDF provided a useful, and successful, framework for both the topic guide in the interviews, and the content analysis, to ensure a wide exploration of the barriers and enablers.

Francis et al, in 2012, documented the impact of the TDF on implementation research. They reported that 23 empirical studies had been published, with 17 investigating the behaviour of health professionals. Ten of the 21 studies described exploratory interview studies designed to identify barriers and enablers. The authors state that the studies provide evidence that the TDF has considerable breadth and cross-disciplinary impact in research about health related behaviour, and that it appears to have succeeded in making psychological theory useful to researchers from a variety of backgrounds internationally. The current study will add to the growing body of evidence, having used the TDF to explore GP behaviour when prescribing for older people with RKF.

4.6.6.2 Future research.

The study findings will help to inform the content and design of an intervention to improve prescribing in reduced kidney function in primary care. The next stage of this programme of research (Chapter 5) was planned to confirm and combine the findings with experts, stakeholders and policymakers in related fields, get an indication of feasibility and acceptability, and prioritise the key themes for an intervention and future research.

Rich data has been collected from the GP interviewees. Analysis was completed for the current project, but the data could be reanalysed in greater depth to gain more understanding of prescriber behaviour generally in primary care.

4.6.7 What this study adds to practice and policy

Complex underlying factors for inappropriate prescribing for older people with reduced kidney function in primary care were found in this study. Highlighting the issues to both clinicians and policymakers is the first stage in minimising inappropriate prescribing in routine clinical practice. It was planned that the final stage of this programme of research would involve experts, stakeholders and policymakers in related fields (Chapter 5). Further research is needed to ensure an intervention will be more likely to be successful in changing practice.

The BNF was a key resource but the chapter on 'prescribing in renal impairment' was not known about and the advice on kidney function equation choice is confusing and so working with the Formulary Committee could help prescribers apply the recommendations.

 'Goal conflict' was expressed where the prescribing recommendations might be seen to go against clinical guidelines. This suggests that the guidelines should make explicit the need to apply parameters such as kidney function to the decision making, for example antibiotic guidelines encourage use of nitrofurantoin for urinary tract infection, but if kidney function is too low it may be ineffective and adverse effects are more likely, and an alternative should be used. It has been recommended in a recent paper from the Guthrie team that guideline developers should particularly consider whether chronic kidney disease is common in the target population (Dumbrek et al, 2015).

4.6.8 Progression and integration of methods and findings

The lack of awareness and knowledge about prescribing in RKF expressed by the GP participants would account for the findings in the case-note review (Chapter 1) where 25% of older people with RKF were on a drug that should be avoided or the dose was too high for their level of kidney function. Also for the results found in the PCT-wide cross-sectional survey (Chapter 3) where 3.5%-39.6% of people aged over 65 years, and 24.2%-79.5% of those aged 85 years and older, had a kidney function too low for the drug or dose they were taking.

Many of the GPs did not recognise the drugs investigated as being affected by kidney function except for metformin and nitrofurantoin. However, in the PCT-wide survey, nitrofurantoin had the highest figures for being used when kidney function was too low.

This may be that being aware has not changed behaviour, or that clinicians have only recently been made aware and the figures might now be improved. Most of the drugs studied were repeat medications where there should be regular review, but the findings in the quantitative studies showed that kidney function was not accounted for and that it was worse in the older age groups, implying that review did not happen.

Kidney function is regularly tested, which was shown in the PCT-wide survey with 82.5-97.2% (depending on the drug) having a recent check, but the GP interviews found that although they tested kidney function, they did not then apply that to prescribing and review.

4.7 Conclusion

To reduce the risk of harm for older people on drugs excreted by the kidney, GPs need awareness, education, and support to apply the prescribing recommendations in reduced kidney function.

'Old age is not the source of our problems; it is where we will find the answers'

Dr William Thomas, 2004

5 Chapter 5: A consensus group method to identify key themes for development of an intervention strategy and future research into prescribing for older people with reduced kidney function.

5.1 Background

Older patients are at greater risk of harm when recommendations for prescribing in reduced kidney function (RKF) are not applied (scoping literature review, Chapter 2). A cross-sectional case-note review (Chapter 1) and PCT-wide prescribing data survey (Chapter 3) in UK primary care found that a quarter of people aged 65 years and older with RKF were on a drug or dose that would not be recommended at their level of kidney function, and the likelihood of having a kidney function too low increases with age. Key areas for change have been highlighted in a GP interview qualitative investigation (Chapter 4).

A formal facilitated group consensus process would allow experts and stakeholders to rate and prioritise the barriers and enablers to applying recommendations on prescribing in RKF, generated from the qualitative GP interview study.

This study aimed to explore the generalisability of findings, generate a strategy for an intervention, and prioritise a strategy for evaluation research.

5.2 Research question and objectives

Research question

Do experts in fields relating to prescribing in reduced kidney function find the evidence from the four programme studies (case-note review, scoping literature review, prescribing data survey, GP interview study) generalisable, what should the strategy be for an intervention, and what are the priorities for future research?

Objectives

- To systematically combine the evidence from the four project studies with expert opinion.

- To explore the opinions of experts in the field on agreement, importance and feasibility for the key themes on what needs to change to improve prescribing for older people with RKF.

- To gain consensus on priorities for intervention and future research.

5.3 Methodology

5.3.1 Consensus method

The 'RAND Appropriateness Method' was used to systematically combine the research evidence, synthesise and clarify expert opinion, generate a consensus, and capture the multidisciplinary perspective (Fitch et al, 2001; Shekelle, 2009; Campbell et al, 2001; Jones and Hunter, 1995; Murphy et al, 1998). The core components of the RAND process have been summarised by Brook et al (1986), Shekelle et al (1996; 1998) and Fitch et al (2001). The key stages of the method are:

- Selection of condition(s) to be assessed.

- Systematic review of the evidence base.

- Generation of indicators/criteria to be rated.

- Selection of expert panellists.

- First round individual rating.

- Panel meeting.

- Second round individual rating.

- Final analyses and development of recommended indicators/criteria.

This 'nominal group' method was chosen as it has been shown to be more effective than an 'interacting group' (Robson, 2011) which involves an initial group discussion on the topic or issue followed by a group assessment. In the nominal group method, respondents make their initial estimates individually, which means there is no effect from other participants such as social pressure and negative group influences, for example dominating members. There is then a panel discussion which results in a group view agreed, followed by a final individual rating.

The 'Nominal Group Technique' (NGT) (Delbecq et al, 1975) is another method cited but is used primarily to generate ideas which can subsequently be rated using, for example, the RAND or Delphi methods.

The 'Delphi' method has been used in prescribing research, for example Cantrill et al (1998) and Campbell et al (2000). It is a technique where individuals make independent estimates or give views about the issue in question. These are aggregated by a central group who provide feedback on the group results to the

individuals. The individuals subsequently confirm or revise their estimates until either a group consensus is reached or an acceptable range of views is achieved. The advantage of the Delphi method is that it does not require individuals to be brought together so the time and cost of participants travelling to meetings is saved, and anonymity of participants preserved. However, the process is time consuming to coordinate and manage and it can be difficult to maintain active participation by participants the whole way through, and so drop outs are more likely than at one off meetings. Also, the decision-making process is less transparent than face to face meetings, and can be more easily influenced by the coordinator (Linstone and Murray, 2003).

In a review on consensus methods in prescribing research, the main benefit found for the RAND method is that it combines expert opinion with evidence in a more quantifiable way than the other approaches, having aspects of both Delphi and NGT (Campbell et al, 2001). For the current study there were key themes that needed to be prioritised so a method that would include statement ratings was required. Also, evidence to be presented for consideration from the project studies was, as yet, unpublished and so the opportunity to present data to the panel group was useful.

5.3.2 Theoretical Domains Framework (TDF) and COM-B model

The GP interview study used the TDF to highlight key themes for change in capability, opportunity, and motivation (the 'COM-B' model). Each domain of the TDF relates to a COM-B component (see Table 5, Chapter 1), providing a framework for a more detailed understanding of the behaviour within the COM-B components (Michie et al, 2014, pp 91-93). In the GP interview analysis (Chapter 4), linking to COM-B components helped to strengthen the understanding of the TDF domains for the non-psychologist researcher, and frame the findings to highlight what needed to change.

The TDF has been used previously in expert panel studies in healthcare, for example Porcheret et al (2014) and Khan et al (2014). The TDF provided the framework for the method and analysis of this consensus panel study, and linking to COM-B components highlighted what needed to change to improve prescribing in reduced kidney function (RKF).

5.3.3 Panel composition

The validity, credibility, reliability, and acceptability of the findings of a consensus method will depend, in part, upon the group composition. Campbell et al (2001) states that the panel must reflect the 'constituency of stakeholders' it is intended to represent.

There should be individuals with relevant knowledge, perspective or experience, or individuals who are highly regarded in the chosen field due to their academic expertise or experience.

Murphy et al (1998) states that in general, having more group members will increase the reliability of group judgement. However, where the group members interact, large groups may cause coordination problems within the group. Although it is theoretically likely that group size will affect decision-making, the effects are subtle and difficult to detect. They state that below about six participants, reliability will decline quite rapidly, while above about 12, improvements in reliability will be subject to diminishing returns.

5.4 Study design

5.4.1 Setting

The first round statement rating was done individually on-line at a time convenient to the panellist. The group exercise and second round rating took place at the University of Leeds.

5.4.2 Participants

To ensure credibility, the research team met to provide a robust process for identification of stakeholders and experts in relevant fields as possible participants. The aim was to include representatives with expertise in as wide a range as possible in the intervention functions and policy categories identified on the Behaviour Change Wheel (Michie et al, 2011), as discussed in Chapter 4 (4.6.3). Having expertise in these categories would make it more likely that the panel would have the knowledge and experience to consider a strategy for intervention covering the components of the behaviour.

It was agreed to attempt to recruit participants from the following fields:

- Renal specialist.
- Elderly care specialist.
- GP expert.
- Pharmacist expert.
- Patient record system (e.g. SystmOne, EMIS), decision support systems representative.
- Resource, guideline, policy representative e.g. BNF.
- Medicines safety expert.
- Psychologist.

5.4.3 Sample inclusion criteria and recruitment

Participants were purposively recruited from the listed categories. They were identified as possible participants by the supervision team, from publically accessible websites, or by word of mouth from other experts in the field. Potential participants were contacted by email with a letter of invitation (Appendix 16, 8.15), consent form (Appendix 17, 8.16), and participant information sheet attached (Appendix 18, 8.17). Where no reply was received, one further email was sent.

A certificate of attendance was provided for all panellists as a recognition of their participation in research (Appendix 19, 8.18).

5.4.4 Method

The key themes derived from the GP interview study on what was needed to change were reviewed using a four stage process.

Stage 1: development of statements for review.

Stage 2: first round statement rating by the expert panel.

Stage 3: expert panel group discussion on the statements.

Stage 4: second round statement rating.

After the stage 1 development of statements for review section, the study design, results, and summary are presented for each of the stages 2-4 in turn.

5.4.5 Ethics and governance

University ethics and NHS/other organisation research governance assurance were granted. NHS ethics approval was not needed as participants were healthcare professionals.

SHREC/RP/512 on 16/3/15 (Appendix 20, 8.19)

Leeds West CCG on 27/5/15 (Appendix 21, 8.20)

Bradford Districts CCG on 27/5/15 (Appendix 21, 8.20)

Leeds Teaching Hospitals on 22/5/15 (Appendix 21, 8.20)

Agreement from NICE (email, Appendix 21, 8.20)

key themes		statements
1	In primary care there is a lack of awareness, knowledge, and understanding about prescribing in the reduced kidney function of older people.	1 There is a need to increase the understanding of prescribers about the relationship between kidney function, blood level, and effect on drugs excreted by the kidney.
		2 There is a need to increase awareness of appropriate use, and dosing, of drugs in reduced kidney function.
		3 There is a need to increase knowledge of the recommendations for prescribing in reduced kidney function, and how to apply them.
		4 Prescribing in reduced kidney function should be taught to prescribers and potential prescribers.
		5 Tailored teaching on prescribing in reduced kidney function is required for specialist practitioners in areas such as diabetes, pain, and anticoagulation.
2	Kidney function testing is required when prescribing for older people.	6 When prescribing drugs excreted by the kidney for older people, kidney function needs to be checked and the result applied for use, and dosing, of drugs.
		7 It needs to be clearer that creatinine clearance (Cockcroft Gault) should be used as the kidney function estimate when prescribing high risk drugs, and for higher risk patients including for older people; rather than eGFR which is an indicator of kidney disease and risk to the kidney.
		8 Calculation of creatinine clearance, and its application, need to be easier in the prescribing process.
3	The application of kidney function level to prescribing decisions is needed at drug initiation and at medication review.	9 Currently warnings and prompts on the patient record system are only flagged when initiating a drug; there need to be warnings and prompts on recommendations highlighted when doing a medication review.
		10 There is a need for a recent kidney function test to be available when doing a medication review as it may have changed since initiation or the previous review.
		11 The sense of responsibility taken for prescribing and monitoring by the clinician needs to be as acute at medication review as it is at initiation, because parameters such as kidney function may have changed.
		12 Computer decision support on home visits would be useful to highlight warnings and prompts.
4	There is difficulty in remembering to apply the recommendations for use, and dosing, of drugs in reduced kidney function.	13 Help is needed to remember which drugs are affected by reduced kidney function and what to do for each.
		14 Prompts are needed to apply the kidney function level when prescribing, as attention is on other things in a consultation.
		15 Warnings and prompts need to be linked to level of kidney function, and be patient and drug specific.
		16 Warnings and prompts need to highlight a low level of kidney function before prescribing decisions need to be made.
		17 The habit of prescribing 'the usual dose that is always prescribed' needs to be broken.
5	There is a need for computer decision support for kidney function assessment within the prescribing process.	18 Computer decision support is needed because prescribing is a multi-step process and polypharmacy increases the complexity.
		19 To reduce the risk of mistakes being made, computer decision support is needed to help apply recommendations on use of drugs in reduced kidney function.
		20 Assessing kidney function for older people should be considered a required part of the prescribing process to reduce the risk of harm.
6	There is limited use and confusion with the resources available to support the use, and dosing, of drugs in reduced kidney function.	21 Prescribers need to be made aware of resources available to help with prescribing in reduced kidney function e.g. BNF, pharmacists, reference materials (leaflet and on-line), phone app, and renal team e-consultation.
		22 The BNF - there is a need to increase awareness of the 'Prescribing in renal impairment' section and a clarification of eGFR vs CrCl with interpretation of the recommendations given in the drug monographs.

Abbreviations: BNF: British National Formulary; CrCl: creatinine clearance; eGFR: estimated glomerular filtration rate.

Table 46: The key themes and 22 statements for rating by the consensus panel.

5.5 Stage 1: Development of statements for review

The GP interview study (Chapter 4) used a content analysis, and the emergent themes were mapped onto the domains of the Theoretical Domains Framework for further analysis. A process of reading and re-reading the themes and quotes in each domain, and analysis of the range, led to the development of six 'key themes' to identify the range of potentially influential determinants, and what needs to change to reduce inappropriate prescribing in RKF.

For the current study, the themes derived from the GP interviews were further analysed within the six key themes to produce statements that could be rated by the expert panel. The final twenty-two statements used for the consensus panel process are listed in Table 46, such as:

2. There is a need to increase awareness of appropriate use, and dosing, of drugs in reduced kidney function.

9. Currently warnings and prompts on the patient record system are only flagged when initiating a drug; there need to be warnings and prompts on recommendations highlighted when doing a medication review.

5.6 Stage 2: First round statement rating

5.6.1 Study design for stage 2

5.6.1.1 Method

An on-line rating process was conducted. The survey was built, data collected, collated, and analysed using the Bristol On-line Survey (BOS, 2015). Panellists individually rated each of the 22 statements for agreement, importance and feasibility on a 5 point Likert scale (where 1 was low and 5 was high) according to their experience, opinion and perception of current practice. The participants were also asked to choose the three statements that they considered to be their top priorities for implementing change. For each statement there was an opportunity to add a comment.

Panellists were emailed the link to their personal on-line survey. Any panellists who had not completed the survey a week before the group discussion were sent a reminder email.

5.6.1.2 Data collection

A 'Bristol On-line Survey' was built to allow individual rating in the participant's own time. This was piloted with 2 supervisors before making available to the consented participants.

5.6.1.3 Analysis

The pre-defined criteria (5.4.3) were used to check that the panel convened was comprised of the required range of expertise.

Quantitative analysis

An ordinal scale was used (1 through to 5) to rank agreement, importance, and feasibility. A '5' is always a more positive rank than a '4', and a '4' more positive than a '3', but the levels are not specified at each point and so there cannot be an assertion that the difference between a '5' and a '4' is necessarily the same as between a '4' and a '3'. This suggests avoidance of measures such as means and standard deviations that treat the intervals as though they are equal. Instead, for each rating, the median was used to measure the central tendency, and a measure of agreement and disagreement to indicate the dispersion of the ratings. 'Disagreement' is defined as 33% or more scores from the sample in both the top (4-5) and bottom (1-2) groups (Fitch et al, 2001).

The results from the Bristol On-line Survey were transferred to Excel to facilitate a quantitative analysis to give a count, median rank and agreement/disagreement for all responses. Consensus was defined as the median score being:

- 1-2 without disagreement – agreement that the statement is 'invalid'
- 3 without disagreement – agreement that the statement is 'equivocal'
- 4-5 without disagreement – agreement that the statement is 'valid'

Qualitative analysis

Participants were able to add comments on the on-line survey and these were thematically analysed to find any new themes that needed to be added to what needs to change, using the TDF and linking to COM-B categories.

5.6.2 Results

5.6.2.1 Demographic analysis

Ten participants were recruited to complete the on-line statement rating out of eighteen invited. There was no reply from 3, and 5 expressed a wish to take part and support for the project but did not have the time or availability.

Representatives from all the fields identified by the research team were recruited for the consensus panel except for having a psychologist. It was agreed by the supervision team that this was less important as the TDF was being used to inform the process.

The final panel included national and regional clinical leads and experience in education, research, computerised decision support, policy, formulary and standard setting (Table 47).

		completed on-line survey	attended group discussion	completed final rating
C1	Renal physician/ AKI national lead	C1	C1	
C2	Geriatrician	C2		
C3	Health informatics analyst	C3	C3	C3
C4	Senior university lecturer/ pharmacist	C4	C4	C4
C5	Renal pharmacist/ DPharm student	C5	C5	C5
C6	Senior hospital pharmacist	C6		
C7	Medicines safety expert pharmacist	C7	C7	C7
C8	NICE pharmacist/ BNF formulary committee member	C8	C8	C8
C9	GP/academic clinical fellow	C9	C9	C9
C10	Renal physician/ Regional lead	C10		

Table 47: Consensus panel participants, who completed each stage, and reasons for non-completion.

5.6.2.2   Quantitative analysis

The results from the Bristol On-line Survey were transferred to Excel to facilitate a quantitative analysis giving count, median rank and agreement/ disagreement categorisation for all responses (Table 48).

There were universally positive 'valid' ratings on agreement and importance for all 22 statements presented to the participants with no 'disagreement' categorisation. Thirteen statements for feasibility had positive median ranks, and nine ranked equivocal, with one categorised as 'disagreement'. None of the 22 statements had a negative 'invalid' median ranking.

Statement 13 was ranked high in all three categories. The consensus was that there was agreement that 'help is needed to remember which drugs are implicated', that it is important, and that it is feasible to implement.

Key themes	Statements for rating	Ranking factors	Rank value			Median rank	Disagreement	Number of participants choosing as a top 3 priority
			Negative 1 - 2	Equivocal 3	Positive 4 - 5			
1. In primary care there is a lack of awareness, knowledge, and understanding about prescribing in the reduced kidney function of older people.	1. need to increase understanding	agreement	2	0	8	4	N	3
		importance	2	3	5	3.5	N	
		feasibility	1	5	4	3.5	N	
	2. need to increase awareness	agreement	0	1	9	4.5	N	6
		importance	0	1	9	4	N	
		feasibility	2	3	5	3.5	N	
	3. need to increase knowledge	agreement	0	0	10	4	N	4
		importance	1	1	8	4	N	
		feasibility	4	2	4	3	Y	
	4. should be taught to prescribers and potential prescribers	agreement	0	0	10	5	N	3
		importance	0	1	9	5	N	
		feasibility	0	3	7	4	N	
	5. tailored teaching required for specialist practitioners	agreement	0	4	6	4	N	1
		importance	2	3	5	3.5	N	
		feasibility	1	4	5	3.5	N	
2. Kidney function testing is required when prescribing for older people.	6. kidney function needs to be checked and the result applied for prescribing	agreement	0	1	9	5	N	1
		importance	0	2	7	4	N	
		feasibility	0	3	5	4	N	
	7. creatinine clearance (Cockcroft Gault) should be used as the kidney function estimate when prescribing	agreement	1	3	5	4	N	2
		importance	1	2	6	4	N	
		feasibility	3	3	3	3	N	
	8. calculation of creatinine clearance needs to be easier in the prescribing process	agreement	1	2	6	4	N	1
		importance	0	2	7	4	N	
		feasibility	2	3	4	3	N	
3. The application of kidney function level to prescribing decisions is needed both at drug initiation and at medication review.	9. there need to be warnings and prompts when doing a medication review	agreement	0	0	10	5	N	3
		importance	0	2	8	4	N	
		feasibility	2	2	6	4	N	
	10. a recent kidney function test should be available when doing a medication	agreement	0	2	8	4	N	2
		importance	1	2	6	4	N	
		feasibility	2	3	4	3	N	
	11. the responsibility taken for prescribing needs to be as acute at medication review as it is at initiation	agreement	0	0	10	5	N	1
		importance	1	2	7	4	N	
		feasibility	2	3	4	3	N	
	12. computer decision support would be useful on home visits	agreement	0	1	9	5	N	1
		importance	0	2	8	4	N	
		feasibility	2	3	5	3.5	N	
4. There is difficulty in remembering to apply the recommendations for use, and dosing, of drugs in reduced kidney function.	13. help is needed to remember which drugs are affected	agreement	0	0	10	5	N	2
		importance	0	0	10	4.5	N	
		feasibility	0	4	6	4	N	
	14. prompts are needed as attention is on other things in a consultation	agreement	0	3	7	4	N	1
		importance	0	3	7	4	N	
		feasibility	1	4	5	3.5	N	
	15. warnings and prompts need to be linked to level of kidney function, and be patient and drug specific	agreement	0	0	10	5	N	1
		importance	0	3	7	5	N	
		feasibility	2	4	4	4	N	
	16. warnings and prompts need to highlight reduced kidney function before prescribing decisions need to be made	agreement	1	2	5	4	N	1
		importance	1	3	4	3.5	N	
		feasibility	0	3	5	4	N	
	17. the habit of prescribing 'the usual dose that is always prescribed' needs to be broken	agreement	0	1	9	4	N	1
		importance	0	4	5	4	N	
		feasibility	3	3	4	3	N	
5. There is a need to embed kidney function assessment within the prescribing process.	18. computer decision support is needed because prescribing is a complex, multi-step process	agreement	0	1	9	4.5	N	1
		importance	0	4	6	4	N	
		feasibility	3	3	4	3	N	
	19. to reduce the risk of mistakes being made, computer decision support is needed	agreement	0	2	8	4.5	N	1
		importance	1	2	7	4	N	
		feasibility	3	3	4	3	N	
	20. assessing kidney function for older people should be considered a required part of the prescribing process to reduce the risk of harm	agreement	1	3	6	5	N	0
		importance	2	3	4	3.5	N	
		feasibility	2	2	5	3.5	N	
6. There is limited use and confusion with the resources available to support the use, and dosing, of drugs in reduced kidney function.	21. prescribers need to be made aware of resources available to help with prescribing in reduced kidney	agreement	1	0	9	4.5	N	0
		importance	1	2	6	4	N	
		feasibility	1	2	6	4	N	
	22. British National Fpormulary recommendations need clarification	agreement	2	2	6	4	N	1
		importance	2	2	5	4	N	
		feasibility	1	2	5	4	N	

Table 48: On-line survey statement ratings as mean rank and standard deviation for agreement, importance, feasibility, and top three priority.

Three more statements were ranked high in two categories. Agreement and importance were ranked high for:

- That prescribing in RKF should be taught to prescribers and potential prescribers (statement 4).
- Warnings and prompts need to be linked to level of kidney function, and be patient and drug specific (statement 15).

Agreement and feasibility were ranked high for:

- Warnings and prompts are needed at medication review (statement 9).

Agreement with the statements

On a Likert Scale of 1 – 5 where '5' is the highest rank of agreement, eight statements had a median rank of '5' with no disagreement:

- That prescribing in RKF should be taught to prescribers and potential prescribers (statement 4).

- Kidney function needs to be checked and the result applied for prescribing (statement 6).

- Warnings and prompts are needed at medication review (statement 9).

- The responsibility taken for prescribing needs to be as acute at medication review as at initiation (statement 11).

- Computer decision support would be useful on home visits (statement 12).

- Help is needed to remember which drugs are implicated (statement 13).

- Warnings and prompts need to be linked to level of kidney function, and be patient and drug specific (statement 15).

- Assessing kidney function for older people should be considered a required part of the prescribing process to reduce the risk of harm (statement 20).

Statements agreed to be important

The highest ratings for the degree to which the statement was thought to be important in implementation of change were:

- That prescribing in RKF should be taught to prescribers and potential prescribers (statement 4) – median rank 5.

- Warnings and prompts need to be linked to level of kidney function, and be patient and drug specific (statement 15) – median rank 5.

- Help is needed to remember which drugs are implicated (statement 13) – median rank 4.5.

Feasibility of the statements

Feasibility was generally rated lower with the highest median rank given being '4'. The statements found to be most feasible with a median rank of '4' were:

- That prescribing in RKF should be taught to prescribers and potential prescribers (statement 4).

- Kidney function should be checked and applied to prescribing (statement 6).

- Warnings and prompts are needed at medication review (statement 9).

- Help is needed to remember which drugs are implicated (statement 13).

- Warnings and prompts need to highlight RKF before prescribing decisions are made (statement 16).

- Prescribers need to be made aware of resources available to help with prescribing in RKF (statement 21).

- BNF recommendations need clarification (statement 22).

Nine statements were ranked equivocally with a median rank of '3'. One of these, the feasibility of increasing knowledge (statement 3), had the only 'disagreement' rating with 4 ranking it negatively and 4 positively. These statements would be explored further in the group discussion.

Priority of the statements

The participants were also asked to choose the three statements that they considered to be their top priorities for implementing change. Only two respondents gave 3 choices (C1 and C9). Three respondents gave 2 choices, two 4 choices, and one gave none whilst one gave 11. Two respondents commented on the survey that they had run out of 'top three' choices:

> "*I started to tick the top priority boxes and then came to the conclusion that all of these elements are important in achieving safer prescribing in the elderly and other patient groups.*" (C10: renal physician with a regional role)

> "*Cannot fit in top 3.*" (C1: renal physician with a national role)

This meant that the 'top 3' were skewed towards the first group of statements (the 'knowledge' theme), however it did give an indication of the main priorities which could be discussed at the panel meeting. The top three priorities ranked were:

- To increase awareness – 6 respondents.

- To increase knowledge – 4 respondents.

- To have warnings and prompts at the medication review – 3 respondents.

- Should be taught to prescribers and potential prescribers – 3 respondents.

- To increase understanding – 3 respondents.

When analysed under setting, role or speciality, 3 of the 4 doctors put increasing understanding as a top 3 priority and all ranked this highly compared to the pharmacists. The doctors also all strongly agreed that the calculation of creatinine clearance should be easier in the prescribing process; again the pharmacists tended to rank this lower.

The primary care practitioners gave strongly agree ratings and top 3 priority for the need for having warnings and prompts at a medication review. They also gave high ratings for the need for the warnings and prompts to be patient and drug specific and to be highlighted before the prescribing decision needs to be made, the latter was not something other respondents ranked as high.

Secondary care practitioners (Renal and Care for the Elderly) agreed strongly that assessing kidney function for older people should be considered a required part of the prescribing process to reduce the risk of harm, whilst primary care ranked it equivocal or disagreed and gave a very low feasibility.

Renal practitioners ranked highly that prescribers should be made aware of resources available and that the BNF recommendations need clarification. The medicines safety pharmacist also ranked highly that the BNF needs clarification and gave it a top 3 priority.

5.6.2.3   Qualitative analysis

Comments added to the on-line survey were thematically analysed to identify new themes.

Most comments were either reiterating their ranking or questioning the premise, or their understanding, of the statement. These would be picked up at the panel discussion meeting, however, there were a few to note:

Capability

On the need to increase understanding, C10 suggested that it was important that awareness was increased of 'Sick Day rules' where medicines are stopped whilst acutely ill to reduce the risk of 'acute on chronic' kidney injury (Griffith et al, 2015). C10 also suggested that:

> *"Hospital blood test reports are not seen in primary care, hence recent episodes of acute renal deterioration may be missed".* (C10, renal physician with a regional role)

When discussing the requirement for education, the need to keep up to date with changes in recommendations was highlighted.

> *"recommendations change and there needs to be a formal process of ensuring these are incorporated into practice….keeping up to date after this is probably more important." (C4, senior university lecturer and pharmacist)*

Opportunity

On the statement regarding having warnings and prompts at medication review, some panel members not working in primary care were unaware that warnings were not available when doing a medication review.

> *"I wasn't aware that such prompts didn't come up on review. Is this true of all systems?"* (C4, senior university lecturer and pharmacist)

Pharmacists were highlighted as health professionals that could help to improve prescribing in RKF.

> *"... pharmacists based in primary care with the skill set to help prescribers*".
> (C5, renal pharmacist)

Questioning the need for change

One respondent, C4, made a few comments that implied they thought there was not a problem in primary care, but which were not in line with the other panellists. This was explored in the group discussion.

> *"Prescribers know where to look if changes in kidney function occur."*

> *"Naively perhaps but I think this is already part of practice in the majority of cases."*

> *"In my experience doses change as function changes if necessary."*

5.6.3 Summary

Panel consensus on agreement, importance and feasibility on what needs to change.

The individual ratings were universally positive on agreement and importance for all 22 statements presented to the panellists, and all but nine statements for feasibility, which were equivocal. This provides a confirmation by the experts and stakeholders for the project findings.

The themes added to the analysis from the on-line survey were:

- That non-primary care participants were surprised that warnings and prompts did not come up at medication review.

- That recommendations change and so there is a need to keep up to date.

- That the role of pharmacists could be increased.

Priorities for intervention strategy and future research.

The top three priorities ranked were:

1. To increase awareness – 6 respondents.

2. To increase knowledge – 4 respondents.

3. To have warnings and prompts at the medication review – 3 respondents.

3. Should be taught to prescribers and potential prescribers – 3 respondents.

3. To increase understanding - 3 respondents.

5.7 Stage 3: Group discussion

5.7.1 Study design for stage 3

5.7.1.1 Method

The expert panel met at Leeds University for a facilitated structured two hour meeting on the themes and statements they had initially rated in Stage 2. The session was led and facilitated by myself. A second researcher (supervisor, LG), experienced in behaviour change theory, attended the group discussion to take notes and verify findings.

The meeting started with a 15 minute presentation by SW to give the panellists an overview of the four studies that have led to the development of the key themes and statements on what needs to change to improve prescribing for older people with RKF. The Power Point slides for the presentation can be found in Appendix 22 (8.21).

The key themes were then presented in turn, with example quotes from the GP interviews. For approximately 1.5 hours, the meeting was structured to facilitate wide discussion on all six key themes, exploration of issues raised, and any new themes raised. Also, issues raised from the on-line survey were discussed.

The discussion was brought to a close 15 minutes before the scheduled end of the meeting to allow time for the final statement rating (Stage 4).

5.7.1.2 Data collection

The group discussion was digitally recorded, with consent, and anonymously transcribed for analysis.

5.7.1.3 Analysis

Demographic analysis

The range of expertise of the panel able to attend the discussion meeting was analysed compared to the agreed pre-defined criteria (5.4.3).

Content analysis

A theory-based, five stage content analysis was conducted on the anonymised transcript from the group discussion meeting (Pope et al, 2000).

Stage 1. Familiarisation

The meeting recording was listened to, and the anonymised transcript was read and re-read to become familiar with the data, and to get an initial impression of the key ideas and recurrent themes.

Stage 2. Identifying a thematic framework

Data was then coded to theoretical domains using the TDF and the emerging themes were mapped to those from the GP interview study, identifying where themes were agreed, disagreed or new themes added. A coding index was developed.

Stage 3: Indexing

The second researcher (LG) used the coding index to code the transcript independently to explore inter-rater reliability.

Stage 4. Charting

The codes and quotes were manually grouped into emerging themes. This was an iterative and reflective process and allowed exploration of intra-rater reliability by re-visiting and refining the coding.

Stage 5. Mapping and interpretation

The emergent themes were mapped and interpreted under each TDF domain, and categorised under capability, opportunity and motivation to structure the findings and to find any differences with participant type. A final analysis was performed to map the findings to the key themes from the GP interview study (Chapter 4) and any new themes added on what needs to change to improve prescribing for older people with RKF (Table 49).

TDF domains	Key themes from the GP interview study	Consensus panel themes
Knowledge	There is a lack of knowledge, awareness and understanding of appropriate prescribing of drugs in reduced kidney function; even if prescribe the Need an understanding of the relationship between kidney function, blood levels of affected drugs and effect it is not taught, either theory or specifics	**K1** Lack of awareness **K2** Lack of knowledge/understanding **K3** Not taught - teaching is important **New theme(s)** **K4** teaching use of the patient record systems useful
Memory, attention and decision process	Understanding makes it easier to remember. Difficult to remember which drugs and what to do for each. Attention is on other things in a consultation. Attention at initiation of a drug and unfamiliar drugs but not at a mediaction review. Not got warnings at a medication review. triggers should be instructive, linked to old age, RKF, drug and want more computer decision support	**M1** warnings and prompts only come up at drug initiation - there are none at review **M2** attention needs to be given to prescribing **M3** kidney function can change so there needs to be review of the prescribing decisions **New theme(s)** **M4** Just need the essential values/ information, in the right place, to make a clinical judgement **M5** a NICE guideline, quality standard etc, on what to do, takes attention and priority away from the visceral response of the prescriber to think about the specific drug in that patient.

Table 49: An example section of the group discussion content analysis mapped onto the TDF domains and linked to COM-B categories, with codes.

5.7.2 Results

5.7.2.1 Demographic analysis

Seven of the original 10 panellists were able to attend the group discussion (Table 47). One of the panellists unable to attend was a second renal physician, and another was a hospital based pharmacist, so there was still the expertise at the discussion meeting. The geriatrician could not attend so there was no elderly care expert for the discussion, but the secondary care clinician expertise was represented.

5.7.2.2 Qualitative analysis

Table 49 shows one section as an example from the content analysis where emerging themes were mapped onto the TDF domains, whether they were themes that reiterated those found in the GP interview study, or whether they were new themes identified. The TDF domains were mapped to the COM-B categories using the Michie et al (2014) linking as previously shown in Table 5.

Themes from the group discussion reinforced those found from the GP interview study (Chapter 4), as well as introducing new themes to be considered on what needs to change to improve prescribing for older people with RKF. The importance and the potential to cause harm was reiterated by the panel:

> *"We all think that it's hugely important! We just don't want to talk about it because we don't really know what we're doing!'"* (C9: GP and academic clinical fellow)

> *"The pen is mightier than the scalpel in terms of the damage that you can do to a patient by writing the wrong drug and the wrong dose for a patient...there's principles there that if these organs are affected then the drugs you're prescribing you may not be giving the right dose."* (C1: renal physician with a national role)

> *"I think we may underestimate how much harm we may be actually doing to patients by having them on the wrong drugs and wrong dosages or the wrong drugs at the wrong time."* (C1: renal physician with a national role)

To explore agreement and consensus for the key themes, example quotes from the meeting are presented:

Key theme 1: in primary care there is a lack of awareness, knowledge, and understanding about prescribing in the reduced kidney function of older people.
It was agreed that there is a need to increase awareness of this issue in prescribing and that there is a knowledge gap.

"I'm not generally a big fan of saying it's about knowledge, but, given the figures, you know, actually you can't do it without that knowledge." (C7: medicines safety expert pharmacist)

"I do also think that there's a knowledge gap here as well, because again I think well why is Cockroft and Gault suddenly a big thing now, so it's kind of tackling that as well as tackling how can we get this information out quickly." (C8: pharmacist with a role in formulary guidance and standard setting)

There was agreement that education and training on prescribing and recommendations in RKF is required at all levels.

"Certainly in terms of general practice training there's quite a comprehensive curriculum that doesn't really talk about prescribing at all." (C9: GP and academic clinical fellow)

"It's about education, and I think doctors can learn these drugs, not necessarily the nuances of every single drug, but they can learn over time…I think it's important that every specialty pays attention to the drugs, say the cardiologists, they use these medications with patients with severe heart failure, they go on to a cocktail of ACEI, furosemide, spironolactone and they get their acute kidney injury." (C1: renal physician with a national role)

Key theme 2: kidney function testing is required when prescribing for older people.

The panel confirmed that when prescribing drugs excreted by the kidney for older people, kidney function needs to be checked and the result applied for use, and dosing, of drugs.

"We can watch the kidney function because we know it can decrease…and we can we can think about the drugs we've already prescribed because it's dynamic." (C1: renal physician with a national role)

After discussion, they all agreed that creatinine clearance calculated using the Cockcroft Gault equation should be used for prescribing decisions for older people, and that it should be easier in the prescribing process.

"I'm absolutely convinced that what we should be using is the Cockcroft and Gault." (C7: medicines safety expert pharmacist)

"I personally feel that Cockcroft and Gault is the standard of what we should be using." (C5: renal pharmacist)

C9, GP and academic clinical fellow, highlighted that the 'renal calculator' needs amending on the patient record system.

"Well it needs making right, it needs making right! And anything that is developed will be freely made available to EMIS or any of the other systems."
(C3: health informatics analyst)

Key theme 3: the application of kidney function level to prescribing decisions is needed both at drug initiation and at medication review.

The problem of warnings and prompts not being available when doing a medication review was re-iterated.

"Those pop-ups only appear when you initiate a drug and once you've gone past that and decided it's on the repeat template you never see that again.'"
(C9: GP and academic clinical fellow)

"When you first write a prescription out for say X and it flashes up…a thing with lots of stars on it telling you you're going to kill someone… And then when you see Mrs Blogs for a repeat prescription, nothing then flags up? You've got a list and you kind of look through it and go yeah that's all okay, push a button, and it's done for another twelve months. So, and nothing else pops up." (C9: GP and academic clinical fellow)

Also the need for a recent kidney function test to be available when doing a medication review as it may have changed since initiation or the previous review.

"Often people write the drug chart, and they forget that it's dynamic and the patient's kidney function can change secondary to something else such as pneumonia, for example." (C1: renal physician with a national role)

"I think if it's been 12 months just leave it alone, but, actually, they've had a creatinine measure in that time, things might have changed, or there might have been other things added." (C9: GP and academic clinical fellow)

C3, health informatics analyst, confirmed that it is now possible to have mobile computer decision support and the panel agreed that would be beneficial for patient safety.

"I have some very scary home visits, because I have to start scratching my head…thinking for myself rather than the computer." (C9: GP and academic clinical fellow)

Key theme 4: there is difficulty in remembering to apply the recommendations for use, and dosing, of drugs in reduced kidney function.

It was agreed that help is needed to remember which drugs are affected by reduced kidney function and what to do for each. Patient and drug specific warnings and

prompts would help direct attention in the consultation and be more useful than those currently presented.

> *"So the vast majority of general practice is done just on implicit knowledge, you know, things don't get looked up, the vast majority of our GPs haven't done the checking out what they know, and what they don't know, in order to treat the patient."* (C7: medicines safety expert pharmacist)

> *"You could make it personal to that patient…in SystmOne they can, I presume in EMIS...you could pick up that patient...a low kidney function test, pick up the age, pick up a frailty, it could do that and set off a template or whatever."* (C3 health informatics analyst)

QOF and other guidance, and policy, have become the priority in the consultation.

> *"There is a hierarchy of focus in general practice and it starts with QOF, and NICE guidance, and if there isn't a piece of NICE guidance about, say, prescribing, then it's the 6th thing on the list."* (C9: GP and academic clinical fellow)

> *"Do you think that approach of almost that visceral response to I need to think about that drug, do you think that's watered down or feels secondary to there's a NICE guideline to what you do if someone's had an MI."* (C9: GP and academic clinical fellow) *"Yeah I do."* (C1: renal physician with a national role)

Key theme 5: there is a need to embed kidney function assessment within the prescribing process.

Discussion around computer decision support centred on the complexity of prescribing. The medicines safety pharmacist (C7) discussed how prompts can also be beneficial in increasing knowledge, and that audit should also be part of the process to find those where kidney function has not been assessed.

> *"Having it embedded means that you get an opportunity to consider it that you wouldn't have necessarily had previously… It's ringing the alarm bells"* (C7)

> *"We know that knowledge based interventions work the majority of the time. That's the way general practice works, you know, they apply what they know, implicit knowledge, every day. But it doesn't work all the time, so then you have to put something else in. And the next step is the prompts at the point where the decision making is made because that will then have an impact on future decisions, increasing knowledge."* (C7)

It was highlighted by the panel that they thought ensuring kidney function levels are applied to prescribing is a patient safety issue at least as important as allergies.

"I think when we've identified that it's awareness, then I think elevating the function to the point of allergy, going actually this is just as important. In fact, you're more likely to hospitalise someone because of their renal function." (C7: medicines safety expert pharmacist)

"I think it's about making it something around patient safety and making us more aware of the importance of it and that it is as important as doing a coronary cath on somebody... it's the interventional stuff that gets people excited but prescribing of drugs it's like oh god do I have to do that drug chart; but no, no, no, this is such an important foundation for this patient's care." (C1: renal physician with a national role)

Key theme 6: there is limited use and confusion with the resources available to support the use, and dosing, of drugs in reduced kidney function.

It was agreed that guidelines need to include advice on use of drugs in RKF, and that resource such as the BNF could be improved to help prescribers apply the recommendations.

"Have you spoken to the BNF about that? … it would be worth passing that on…I would write to them because it will be considered." (C8: pharmacist with a role in formulary guidance and standard setting)

Pharmacists were highlighted as a helpful resource.

"And if there are pharmacists based in practices, and focussed on the medicine, then they could do the medicine review, and, by doing that, that will also increase the GPs awareness to focus on problem drugs." (C5: renal pharmacist)

"I think pharmacists would be in an ideal position to look at the detail." (C8: pharmacist with a role in formulary guidance and standard setting)

Additional themes elucidated

New themes came from the consensus panel discussion that were mapped onto the TDF domains. The themes in the TDF domains were categorised to the 'COM-B' model (Michie et al, 2014; Table 5) to frame the themes into what needed to change and allow future analysis and intervention development using the Behaviour Change Wheel.

Capability

Teaching use of the patient record systems is useful so that prescribers are aware of how the technology can help.

"Those modules [on use of SystmOne] in the undergraduate course – they've been phenomenally well received out in the community… simply because we now have students who are IT record literate." (C9: GP and academic clinical fellow)

Cyclical audit can focus on the problem as well as 'mop-up' cases that have been missed.

"If you're looking at it as managing risk in a practice then cyclic audit... it really focuses the mind on the problem that you're trying to solve, reducing the medicines burden for patients with renal disease." (C7: medicines safety expert pharmacist)

Ideal weight (or lower if actual) should be used in the CrCl-CG calculation.

"I think it's got to change - it uses actual weight not ideal weight." (C5: renal pharmacist)

"The calculator uses actual weight not ideal weight." (C9: GP and academic clinical fellow)

Opportunity

There is a large impact of the findings because of the scale of prescribing, most of which is in primary care.

"Most prescribing is in primary care, a vast amount of prescribing." (C4: senior university lecturer and pharmacist)

Pharmacists could take on roles such as medication review and audit.

"There is a need to increase knowledge and understanding in primary care, and it's about increasing awareness as well, so...if there are pharmacists based in practices, and focussed on the medicines, then they could do the medicine review, and, by doing that, that will also increase the GPs awareness to focus on problem drugs." (C5: renal pharmacist)

"There's lots of issues around medication and polypharmacy isn't there at medication reviews, I think pharmacists would be in an ideal position to look at the detail." (C8: pharmacist with a role in formulary guidance and standard setting)

If community pharmacists had access to blood results it would be another check, and would also allow them to review the medication use.

"…community pharmacists being able to access blood results as well as being like another layer in the check when giving out prescriptions." (C5: renal pharmacist).

Motivation

Renal medicine hasn't been seen as part of the GP role. It used to be managed in secondary care but now has moved out to primary care.

> *"I think the place where chronic kidney disease is managed has changed over the years as well, more and more of CKD 3 and 4 is moved out to the community whereas it used to be a specialty managed condition."* (C9: GP and academic clinical fellow)

A trigger or prompt on the medication list screen at eye level is most likely to be useful (like allergies but higher up on the screen).

> *"Your eyes are in the middle of the screen and you're thinking about which drug should I choose - I'd like that to be right under where you type in the drug name…where I type the drug name, right underneath it is, or even just above it, is your allergy status, here's your renal function status"* (C7: medicines safety expert pharmacist)

National guidance, quality standards etc. act as a lever, they are transformative, providing a priority focus and leading to the teaching curriculum and e.g. QOF.

> *"I don't know what a NICE guidance would look like around drug prescribing but … it then affects the curriculums [teaching – NICE]...It's a lever...It's transforming acute kidney...It just focuses the mind, I couldn't get people to take it seriously until we had the NICE guidance and suddenly it became an issue."* (C1: renal physician with a national role)

> *"The lovely thing about NICE guidelines is it forms a focus."* (C4: senior university lecturer and pharmacist)

A published guideline is not enough to cause action, an intervention is needed to enact the guidance.

> *"I don't see a direct relationship between what NICE publish and what GPs do. It's the intervention that other people put in, in order to enact the NICE guidance in primary care."* (C7: medicines safety expert pharmacist)

Patients are unaware of RKF.

> *"I mean it is more of a hidden disease, in the consultation we talk about diabetes and heart attacks and knee pain, and it might be in the clinicians mind that they have to think about renal function but not the patients."* (C9: GP and academic clinical fellow)

> *"I would think it's a very low proportion of patients who know that they have reduced kidney function."* (C5: renal pharmacist)

Statements on feasibility not positively ranked in Stage 1

The feasibility statements ranked as equivocal on the on-line survey were explored by the discussion group. There was agreement across the panel, after discussion, that CrCl-CG should be used for prescribing decisions and that it should, and could, be made easier for prescribers in an intervention. Teaching of current and new prescribers was agreed as important to increase knowledge. Use of patient and drug specific prompts and warnings could help to break habit.

5.7.3 Summary

The panel discussion confirmed the agreement, importance and feasibility of the key themes on what needs to change. Even the statements where feasibility had not been positively ranked in the on-line survey were felt to be important and that there would be ways of making them possible, despite being difficult to design and implement. New themes to be added to the overall analysis were:

Capability

- Teaching use of the computer patient record system is useful.

- Cyclical audit can focus on the problem, and mop up those not presenting opportunistically.

- Ideal weight (or lower if actual) should be used in the CrCl-CG calculation.

Opportunity

- Prescribers and patients need to be aware that pharmacists can have an increased role in medication review.

Motivation

- Renal medicine has not been seen as a GP role.

- National guidance, quality standards etc. act as a lever and focus priority.

- A trigger/prompt on the medication list screen at eye level would be useful.

- Patients are unaware of kidney function.

5.8 Stage 4: Second round statement rating

5.8.1 Study design for stage 4

5.8.1.1 Method

The panellists repeated the rating of the statements at the end of the discussion meeting. They individually indicated their top 3 priorities for an intervention and

research strategy. The 6 key themes were placed up on a board with the relevant statements listed below. Panellists indicated their first, second and third choice priorities for intervention and future research. They could choose whether their choices were to be anonymous.

5.8.1.2 Data collection

The final statement rating was done by using 'post-it notes' (Figure 34). Each panellist was asked to indicate next to the appropriate statement their first priority with a pink 'post-it note', their second priority with a yellow 'post-it note', and their third priority with an orange.

5.8.1.3 Analysis

Demographic analysis

The pre-defined criteria were used to check that the panellists who completed the stage 3 rating were comprised of the required range of expertise (5.4.2).

Quantitative analysis

A visual analysis of the colours and spread of the post-it notes was followed by a repeat analysis of the top 3 priority choices for intervention and future research.

Qualitative analysis

Comments were added to some of the 'post-it notes' and these were read and analysed in case they added anything further to the final analysis.

5.8.2 Results

5.8.2.1 Demographic analysis

Six panellists completed the final statement rating as the renal physician had to leave the meeting early (Table 47). There was still clinician, secondary care, and renal expertise representation for the final statement rating, as well as the primary care, medicines safety, health informatics, and standard setting/formulary experts.

key theme	statements for rating	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10	Number of participants choosing as a top 3 priority pre discussion	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10	Number of participants choosing as a top 3 priority post discussion
1	1. need to increse understanding	✓	✓							✓		3											
	2. need to increase awareness	✓			✓		✓	✓	✓	✓		6				1	1		2		1		4
	3. need to increase knowledge	✓	✓		✓			✓				4								1			1
	4. should be taught to prescribers and potential prescribers		✓		✓			✓				3			1 b								1
	5. tailored teaching required for specialist practitioners				✓							1											
2	6. kidney function needs to be checked and the result applied for prescribing					✓						1					2						1
	7. Cockcroft Gault should be used as the kidney function estimate when prescribing		✓		✓							2								2	3		2
	8. calculation of creatinine clearance needs to be easier in the prescribing process.							✓				1				1							1
3	9. there need to be warnings and prompts when doing a medication review.				✓		✓		✓			3								4			1
	10. a recent kidney function test should be available when doing a medication review					✓		✓				2				1		3					2
	11. The responsibility taken for prescribing needs to be as acute at medication review as at initiation							✓				1											
	12. Computer decision support would be useful on home visits					✓						1											
4	13. help is needed to remember which drugs are affected						✓		✓			2				3							1
	14. prompts are needed as attention is on other things in a consultation				✓							1			1 a				1				2
	15. warnings and prompts need to be patient and drug specific				✓							1				1							1
	16. warnings and prompts need to highlight RKF before prescribing decisions need to be made				✓							1											
	17. the habit of prescribing 'the usual dose that is always prescribed' needs to be broken					✓						1											
5	18. computer decision support is needed because prescribing is a complex, multi-step process				✓							1								2			1
	19. to reduce the risk of mistakes being made, computer decision support is needed				✓							1											
	20. assessing kidney function a required part of the prescribing process to reduce the risk of harm											0				1				3			2
6	21. prescribers need to be made aware of resources available											0											
	22. BNF recommendations need clarification				✓							1											
Other	23. use pharmacists														3	2							2
	24. NICE/ general prescribing guidelines - what needs to be thought about, in what groups etc														2								1

Abbreviations: BNF: British National Formulary; NICE: National Institute for Health and Clinical Excellence.

Table 50: top 3 priority ratings pre and post group discussion.
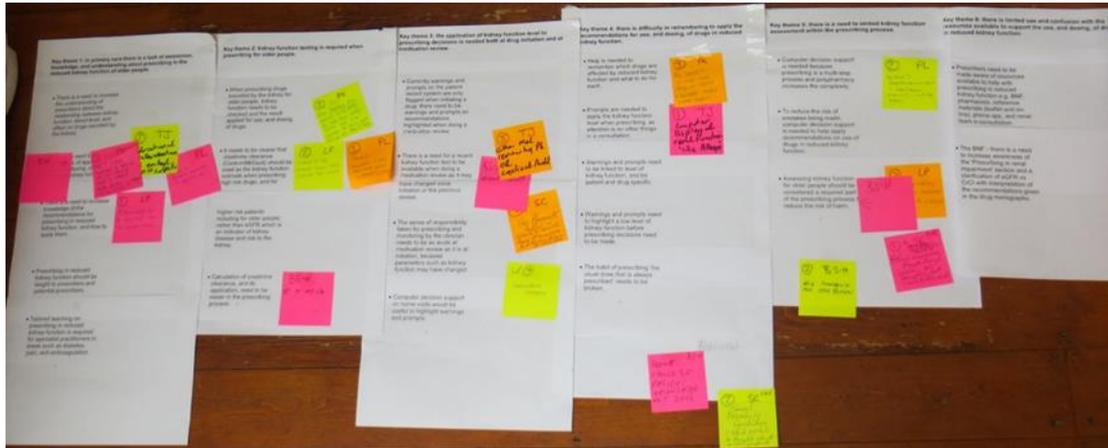
Figure 34: Consensus panel top three priority rating by post-it note.

5.8.2.2 Quantitative analysis

A clear top priority was given for the need to increase awareness with three 1st choice rankings and one 2nd. The second priority shown was for 'warnings and prompts needed' with two 1st choices. Two statements had one 1st and one 3rd choice and so were the next placed priority choice: that a recent kidney function test should be available at medication review, and assessing kidney function for older people should be considered a required part of the prescribing process to reduce risk of harm (Table 50).

The panellist choices were spread across five of the six themes, as shown in the picture of the key theme listings taken from the board (Figure 34). There was one main cluster on the first sheet which was 'need to increase awareness'. Although no top priority choices were places on key theme 6 at the end, there had been discussion on resources prior to the final rating, and it had been agreed that the BNF needed clarification to help prescribers implement recommendations on prescribing in RKF.

Despite the discussion and explanations on what was requested, one participant said they couldn't chose and needed four choices and another also said they couldn't choose and decided they were going to give a 'number 1' in each of 5 key themes.

When analysed for role, setting and speciality, no pattern was detected.

5.8.2.3 Qualitative analysis

The notes added to the 'post-it-note' choices were:

Capability

- 'Educational intervention to embed top ten culprits.'

Opportunity

- 'Links to SPC/renal database and links to secondary care.'

- 'Medication review by pharmacists and cyclical audit.'

- 'Computer display of kidney function like allergies.'

- 'Prompts though systems not proscriptive – need to be thought about.'

- 'Prompts should be patient orientated.'

5.8.3 Summary

Top priority for an intervention and future research was given for the need to increase awareness. The second priority was for 'warnings and prompts needed as attention is on other things in a consultation'. Two statements were the third placed priority choice: that a recent kidney function test should be available at medication review, and assessing kidney function for older people should be considered a required part of the prescribing process to reduce risk of harm.

The need for intervention was considered as important because of the risk of harm to older people. Prompts should be drug and patient specific, computer display more usefully placed, and education and resources improved. Pharmacists could be involved more in medication review and cyclical audit.

5.9 Discussion

5.9.1 Principal findings

An expert panel, with a wide breadth of experience and expertise in a range of BCW intervention functions and policy categories, gave support for the project findings. The top priorities for intervention and research were identified as:

- There is a need to increase awareness.
- Patient and drug specific warnings and prompts are needed.
- Kidney function assessment for older people should be a required part of the prescribing process to reduce risk of harm.
- A recent kidney function test should be available at medication review.

The universally positive ratings on agreement and importance for all 22 statements, and the majority for feasibility, on the individually rated on-line survey provides a confirmation by the experts and stakeholders for the results from the GP interview study (Chapter 4). This was reinforced in the group discussion. The panel recognised the findings that many older patients are prescribed drugs when their kidney function

was too low for it to be appropriate, and which supported the current broader evidence found in the scoping literature review (2.5); for example, the primary care studies in France (Breton et al, 2011) and Australia (Khanal et al, 2015), and the UK hospital based study (Jones and Bhandhari, 2013).

The Panel group discussion also endorsed that the importance of the statements was because of the consequent risk of harm caused by inappropriate prescribing in RKF, as found in the scoping literature review (2.7); for example increased mortality (Breton et al, 2011), hospital admissions (Helldén et al, 2009), and increased risk of ADRs (Corsonello, 2012). It was suggested in the panel discussion that patients were more likely to be hospitalised from ADRs from not applying the recommendations in RKF than for allergies, and that it should be given the same importance. The renal consultant with a national role suggested the findings should be framed as a safety issue.

The scoping literature review (2.6) found evidence that the Cockcroft Gault equation should be used to estimate CrCl kidney function when making prescribing decisions for the older patient (Melloni et al, 2008; Roberts et al, 2008; Spruill et al, 2008; Hellou, 2010). At the group discussion there was unanimous agreement with this finding, and doctors strongly agreed that 'the calculation of CrCl should be easier in the prescribing process'.

A top 3 priority was given by the panel that warnings and prompts are needed at medication review. This was a key theme identified from the GP interview study that hadn't been identified previously as a problem, and had not been found in the scoping literature review. Implementing this would have a spill-over effect for all other warnings and prompts if they can be highlighted at medication review, for example liver function status. The scoping review of intervention evaluation to aid prescribing in RKF (2.10) did find evidence for use of alerts and more sophisticated CDSSs, but there were mixed results in a systematic review (Tawadrous et al 2011). Only 2 of 5 studies looking at patient-important outcomes from computerised CDSSs were beneficial. However, none of the studies found aiming to improve inappropriate prescribing in RKF were based on theory or determinants of why recommendations were not applied, which might be a factor if the intervention was not addressing where the barriers are. This study has aimed to explore the determinants using behaviour change theory so that an intervention can be developed to address what needs to change in practice.

In the scoping review (Chapter 2, 2.10), however, studies that involved pharmacists in the intervention showed universally positive results, for example, alerts to pharmacists significantly reduced errors for prescriptions in RKF in a large primary care RCT in the USA (Bhardwaja et al, 2011). Pharmacists were highlighted by the consensus panel as a resource for doing medication review, providing education and training, and for audit. Cyclical audit was a panel suggestion that can focus on the problem, and mop up patients not presenting opportunistically. The consensus panel also suggested that both prescribers and patients need to be aware that pharmacists can have an increased role in medication review. It was also suggested that if community pharmacists had access to blood results it would be another check, and would also allow them to review the medication use. In the Netherlands Geerts et al (2013) showed it was feasible for community pharmacists to test kidney function and advise GPs where needed, having previously shown a benefit for patients if they had access to kidney function results (Geerts et al, 2012).

The 'PINCER' study (Avery et al, 2012) showed that pharmacists can be effective in reducing a range of medication errors. A Cochrane review (Nkansah et al, 2010) found forty-three studies which evaluated non-traditional roles of pharmacists. In general, the data included in this review supported the roles of pharmacists in patient counselling, therapeutic management, and providing health professional education with the goal of improving patient process of care and clinical outcomes. Non-traditional roles of outpatient pharmacists improves health care outcomes. The data showed that educational outreach visits may impact physician prescribing patterns. This Cochrane review is currently being updated (Watson et al, 2015).

No studies were found in the scoping review (0) that explored the determinants for why prescribers do not apply the prescribing recommendations in RKF. There were primary care qualitative studies that found complex interactive factors for inappropriate prescribing in general, such as Slight et al (2013) and Anderson et al (2015), but the GP interview study (Chapter 4) was able to explore the determinants specific to prescribing in RKF, and the consensus panel has gone a step further in getting expert guidance to prioritise the complex findings.

5.9.2 Comparison of responses by panellists

The doctors on the panel ranked 'increasing understanding' as a top 3 priority compared to the pharmacists, who ranked it lower. The doctors also all strongly agreed that the calculation of creatinine clearance should be easier in the prescribing

process, whilst the pharmacists again ranked this lower. The findings suggest that pharmacists may overestimate GP understanding.

The primary care practitioners gave 'strongly agree' ratings and top 3 priority for the need for having warnings and prompts at a medication review and high ratings for the need for the warnings and prompts to be patient and drug specific and to be highlighted before the prescribing decision needs to be made. This had not been recognised as a problem by the other panellists, reiterating the incredulity expressed that this does not already happen.

Secondary care practitioners (Renal and Care for the Elderly) agreed strongly that assessing kidney function for older people should be considered a required part of the prescribing process to reduce the risk of harm, whilst primary care ranked it equivocal or disagreed and gave a very low feasibility. After the group discussion it was a top 3 priority for intervention; the health informatics expert had explained how the patient record system could be improved to use the data already available.

Renal practitioners ranked highly that prescribers should be made aware of resources available and that the BNF recommendations need clarification. The medicines safety expert also ranked highly that the BNF needs clarification and gave it a top 3 priority. This became a group agreement at the discussion meeting.

5.9.3 Engagement in the research

Fifteen out of the eighteen experts invited to participate responded positively with support for the project and a willingness to take part. This response shows a concern for prescribing safety and reducing risk of harm. The final panel included national and regional clinical leads and experience in education, research, computerised decision support, policy, formulary and standard setting.

The numbers involved at each stage of the study fit with the Health & Technology Assessment (Murphy et al, 1998) and re-iterated by Campbell et al (2001) in that the numbers did not exceed 12, and did not drop below 6 for the final rating stage. At each stage there was a range of expertise lending weight to the findings of the panel; even though the number panellists had reduced to six for stage 3, they included representatives from clinical practice, policy, safety, and health informatics.

5.9.4 Strengths and limitations

The range of expertise on the panel, and the methodological rigour used for the process, gives credibility to the findings. Panellists stated that it was useful to have the

initial statement rating phase as it got them thinking about the subject and allowed them to start formulating questions for the discussion. One participant remarked that:

> *"The fact that we have covered all of these different areas is really important. The fact that we haven't just gone down a 'prompts will solve this problem' route."* (C8: pharmacist with a role in formulary guidance and standard setting)

This also recognises how the use of the Theoretical Domains Framework to structure the analysis enabled a wide exploration of the behaviour in the GP interview study. Linking the analysis to COM-B provided a model to strengthen the understanding of the TDF domains for non-psychologist healthcare professionals, structure the discussion around the key themes, and frame the findings to highlight what needed to change to improve prescribing in RKF.

However, the consensus method may have just provided a snap-shot of current opinion (Campbell et al, 2001). Sometimes there can be low levels of agreement, but this was not the case in this study. Some aspects of the process may have been difficult. The participants were given only a short few sentences on the results from the studies in this research for the initial rating so responses were mainly based on their experience in this field. Choosing the top 3 statements as priorities for implementing change proved difficult for some participants, even after the group discussion. The instructions may have been unclear, the structure may have made it difficult, or maybe it was not easy to choose. However, even though it was not as specific as it would have been if all participants had chosen just three, it did give a clear indication of where initial plans for intervention and research should be directed.

There was no patient or public involvement in this study. Members of the panel brought up in the discussion that patients do not have awareness of kidney function. This needs to be explored further and patients will be included in ongoing research.

5.9.5 What this study adds to the literature

An expert consensus panel has considered the findings from the four studies in this project. The scoping literature review (Chapter 2) did not find any quantitative or qualitative UK primary care based studies on prescribing for older people with reduced kidney function (RKF). The expert panel has clarified and aggregated opinion to reach a consensus on priorities for intervention and future research.

5.9.5.1 Consensus methods in prescribing research

The RAND Appropriateness Method has been used in healthcare research to develop quality indicators and review criteria, for example, Avery et al (2011) and Spencer et al

(2014) used it to develop prescribing-safety indicators to assess the safety of prescribing by GPs for the purposes of revalidation. Campbell et al (1999) developed review criteria for assessing the quality of management of stable angina, adult asthma and non-insulin dependent diabetes mellitus in general practice, and To et al (2010) used it to define indicators of primary care for asthma. Campbell et al (2001) state that they believe consensus methods have an important and useful role to play in prescribing research for enhancing decision-making and aggregation into refined agreed opinion. This study has added to the evidence for the method by using it effectively to gain consensus to prioritise a strategy for intervention and research.

5.9.5.2   Use of the Theoretical Domains Framework (TDF) and COM-B

New themes found from the consensus panel discussion were mapped onto the TDF domains. These were linked to the 'COM-B' model to frame the themes into what needed to change and inform future analysis and intervention development using the Behaviour Change Wheel guide developed by Michie et al (2014). Cadogan et al (2015), for example, have identified key TDF theoretical domains and then 'Behaviour Change Techniques' (BCTs) directly. They explored how to improve polypharmacy for older people in primary care. The authors analysed data from semi-structured interviews using TDF domains, identified key theoretical domains, and then identified and selected BCTs by mapping to the TDF. The authors report that all the TDF domains were found to be relevant except 'emotion', which illustrated the complex nature of the behaviour, and the challenge faced in identifying key domains to target for intervention development. They discuss that, despite the intended nature of the TDF to simplify psychological theory and make it more accessible to researchers, there are challenges in operationalising the TDF, particularly around the 12 and 14 domain versions, and in selecting BCTs where they found limitations and lack of consensus.

Linking the analysis to COM-B provided a model to strengthen the understanding of the TDF domains for non-psychologist researcher, structure the discussion around the key themes, and frame the findings to highlight what needed to change to improve prescribing in RKF. It is planned that the guidance provided in 'The Behaviour Change Wheel. A Guide to Designing Interventions' (Michie et al, 2014) will inform the ongoing research project to develop an effective intervention to improve prescribing in RKF.

This study adds to the literature by successfully using the TDF/ COM-B to analyse behaviour in a clinical setting using a consensus group method. The TDF has been used previously in expert panel studies, for example Porcheret et al (2014) where a consensus exercise was undertaken with healthcare professionals to develop a model

for osteoarthritis consultations. Khan et al (2014) proposes using the TDF and a modified Delphi approach in a multi-stage process to develop an online decision support tool.

5.9.5.3 Future research.

The top 3 priorities for intervention and research were identified as increasing awareness, patient and drug specific warnings and prompts needed, and kidney function assessment for older people should be a required part of the prescribing process.

Increasing knowledge was a top ranked statement in the first round rating, but not in the second. However, it was clearly important from the group discussion, as was the importance of teaching prescribers, both new and clinical specialists.

There is now a strategy for post-doctoral development of an intervention and future research. Focus will be on application for funding for a feasibility study, followed by research on an intervention to improve prescribing in reduced kidney function, particularly for older people.

Rich data has been collected from the consensus panel. Analysis was completed for the current project, but the data could be reanalysed in greater depth to gain more understanding of general prescriber behaviour in primary care and how to improve patient safety.

5.9.6 What this study adds to practice and policy

The scoping review of guidelines and resources (0) highlighted that national and international policies and guidance have advised on management of kidney disease but do not cover dosing of drugs that need altering in the reduced kidney function of the older patient. Also that the introduction of a different kidney function estimation equation for eGFR (MDRD) has not been clarified in relation to use for prescribing decisions for older people.

The consensus panel had expertise in NICE guidance, policy development, and the BNF. They suggested working with the BNF Formulary Committee to clarify the guidance on 'prescribing in renal impairment' and the advice on kidney function equation choice.

The panel also suggested that NICE guidance should be clearer on use of medications where parameters such as kidney function are not normal. A recent study has recommended that guideline developers should particularly consider whether chronic kidney disease is common in the target population (Dumbrek et al, 2015). There was

discussion that a NICE guideline on prescribing for older people would be useful, not only to give the latest evidence, but also to provide a lever and a focus for change and the education curriculum.

Pharmacists were highlighted by the consensus panel as a resource for doing medication review, and providing education and training.

Post-doctoral work will include liaison with health informatics to ensure the kidney function calculators are correct on national patient record systems.

Priorities for change have been identified to inform development of an intervention that has the potential to be useable, feasible and effective in changing prescriber behaviour. Highlighting the issues to both clinicians and policymakers is the first stage in minimising inappropriate prescribing in routine clinical practice.

5.9.7 Progression and integration of methods and findings

The consensus panel concurred with the findings of lack of awareness and knowledge about prescribing in reduced kidney function (RKF) expressed by the GP participants in Chapter 4. This would account for the findings in the case-note review (Chapter 1) where 25% of older people with RKF were on a drug that should be avoided or the dose was too high for their level of kidney function. Also for the results found in the PCT-wide cross-sectional survey (Chapter 3) where 19% of people aged over 65 years on the investigation drugs had a kidney function too low, and 39% of those aged 85 years and older.

The GP interview study highlighted that warnings and prompts are not currently available at medication review which is likely to be a factor in the findings in the quantitative studies (Chapters 3 and 4). This had strongly agree ratings from the primary care expert panellists, and was given a top 3 priority for intervention and future research by the consensus panel in the final rating.

5.10 Conclusion

An expert panel gave support for the findings from this project, there is generalisability and acceptability, and change is needed to reduce the risk of harm for older people.

"We all think that it's hugely important! We just don't want to talk about it because we don't really know what we're doing!'"

Participant C9, GP and academic clinical fellow (2015)

"I think we may underestimate how much harm we may be actually doing to patients by having them on the wrong drugs and wrong dosages or the wrong drugs at the wrong time."

Participant C1, renal physician with a national role (2015)

6   Chapter 6: Discussion and conclusion

This PhD programme developed from observations in practice that recommendations for drug use when kidney function is reduced did not seem to be applied for prescribing in primary care. The research studies conducted have systematically investigated the extent of the problem, and explored the underlying determining factors.

Sections 6.1.1-6.1.4 present the findings from each stage of the research, and how they fulfil the research aims.

Sections 6.2-6.4 discuss how the intervention priorities identified need to be assessed in relation to the current evidence found in the literature review. Also, how the intervention priorities need to be considered as to how they might be developed into an intervention that encompasses, and works with, contextual drivers of behaviour relating to prescribing for older people, as well as with current national policies in the NHS. Finally there is a discussion on the next steps that will need to be taken towards intervention development, assessing intervention functions, relevant policy categories, behaviour change techniques (BCTs) and mode of delivery.

6.1   Principal findings for the research aims

6.1.1   Prevalence of inappropriate prescribing in RKF

Inappropriate prescribing for older people with reduced kidney function was found to be widespread. The initial case-note review found that a quarter of the older people were prescribed at least one drug that needed altering or review because of the reduced level of their kidney function indicating that recommendations are not applied for many people. A wide range of drugs were found to be prescribed inappropriately, whether because they should be avoided in RKF, the dose should be reduced, they

are ineffective in low kidney function, or non-specific caution because they are known to cause adverse drug reactions RKF.

No studies were found in the scoping literature review that would give prevalence data in UK primary care for inappropriate prescribing in RKF. However, evidence from other countries, and from the hospital setting, showed many other examples of prescribing where kidney function was too low for the drug, and that this can lead to significantly increased all-cause mortality (Breton et al, 2011), adverse drug reactions (ADRs) (Corsonello et al, 2005), and increased risk of hospital admissions (Helldén et al, 2009) in older people.

The lack of UK primary care prevalence data found led to the cross-sectional PCT-wide survey informed by the case-note review findings. The results corroborated the high prevalence in a wide population as recommendations for use in RKF were not followed for the 8 representative drugs prescribed. For all the older age bands studied, there was prescribing of the drugs found where the kidney function was too low for recommended use, particularly for those aged 85 years and older.

The numbers of older people found taking the study drugs were large, and the fact that the Bradford population has a lower proportion of older people than the national average could mean that the findings might be an underestimate for the wider population. Kidney function tended to reduce with increasing age in the PCT-wide survey, and increased age meant a higher odds of having a kidney function lower than recommended for the drug prescribed.

UK experts in relevant fields concurred with the prevalence findings in the consensus study. They confirmed that the studies described in this thesis have systematically investigated the size and nature of the evidence base, the UK primary care prevalence, and found frequent inappropriate prescribing for older people with reduced kidney function.

6.1.2 Choice of kidney function estimation equation

When comparing the kidney function estimations using the two equations, eGFR and Cockcroft Gault, substantial differences were found when applied to prescribing decisions for the older people reviewed in the case-note review, and subsequently in the PCT-wide cross-sectional survey. Using eGFR as an estimation of level of kidney function was found to identify a much lower number of alterations required for drug or dose choice than would using Cockcroft Gault. Altering or stopping drugs where needed would be missed if eGFR was used rather than Cockcroft Gault in a large

proportion of the patient drug events assessed. This was similar to the many studies found in the evidence from hospital and other countries in the scoping review.

Scoping review studies that looked at patient outcome and drug blood level data agreed that the Cockcroft Gault calculation should still be used to estimate kidney function for drug dosing decisions, in particular for the older patient (Melloni et al, 2008; Roberts et al, 2008); eGFR substantially over-estimates the effect of RKF on drug blood levels and so risk of harm is increased.

There was unanimous agreement by the consensus group expert panel for the need to use creatinine clearance calculated using Cockcroft Gault for prescribing decisions, and the clinicians strongly agreed that the calculation of creatinine clearance should be easier in the prescribing process.

6.1.3 Determinants for why GPs do not apply the drug licence recommendations when prescribing for older people with RKF

No studies were found in the scoping review that aimed to explore the underlying behaviours and determinants of why the recommendations for prescribing when kidney function is reduced are not applied. The qualitative interview study with GPs revealed that there is little awareness of the issues around prescribing and RKF, substantiating the quantitative study findings. Many of the GPs did not recognise the drugs investigated as being affected by kidney function, even by those with a specialist interest in the relevant clinical area. Kidney function was reported as being regularly tested, which was evident in the PCT-wide survey, but the GP interviews found that although they tested kidney function, they did not then apply that to prescribing and review.

Increasing awareness and education is needed for all prescribers, and in clinical specialities, on prescribing renally excreted drugs. Patient and drug specific warnings and prompts at both drug initiation and at medication review would be useful as a reminder when kidney function needs to be taken into consideration. GPs see prescribing safely as an important role, and there was an understanding that harm can be caused by drugs when kidney function is low, but they were not confident in their abilities to apply the recommendations for prescribing in RKF. Resources are used, but the BNF information needs clarifying as the front section on 'prescribing in renal impairment' was not known about and the advice on eGFR versus creatinine clearance is confusing. Evidence found suggests that the BNF guidance is not adequately evidence-based, because of the over-estimation of kidney function when

eGFR is used in older people; also that guidelines could be improved to include advice on use of the relevant drugs when kidney function is low.

The consensus expert panel concurred with the findings of lack of awareness and knowledge about prescribing in RKF expressed by GPs. They also strongly agreed that warnings and prompts should be available at medication review, and was given a high priority for intervention and future research.

6.1.4 Priorities for intervention and research

The top four priorities for intervention and future research were agreed in a consensus process by experts in relevant fields as:

- Increasing awareness of the need to assess kidney function for prescribing.

- Patient and drug specific warnings/prompts are needed at medication review as well as initiation.

- Kidney function assessment for older people should be a required part of the prescribing process.

- A recent kidney function check needs to be available at medication review.

Pharmacists were highlighted by the consensus panel as a resource for doing medication review, providing education and training, and for audit. This was also a finding in the scoping review where studies evaluating interventions to improve prescribing in RKF that involved pharmacists showed positive results.

6.2 The intervention priorities with respect to known intervention studies on improving prescribing in reduced kidney function

For 30 studies identified in the scoping literature review for evidence of intervention evaluation to aid prescribing in reduced kidney function (Section 0), there was no indication of a theory base to inform their intervention development. Not understanding the determinants related to prescribing in RKF might be a factor for studies showing no benefit. Even studies showing a positive outcome from the intervention tested, can be shown to have flaws that indicate the intervention is not likely to be addressing all the factors that have been highlighted from the GP interview and consensus panel studies.

The results might have been improved and been sustainable, if more barriers, or more relevant barriers, had been identified and addressed.

In the following sections the intervention priorities agreed by the consensus group panel are discussed in relation to the intervention studies identified in the scoping review.

6.2.1 Need to increase awareness of the necessity to assess use and dosing of drugs in reduced kidney function

Studies found showed that just having a kidney function level reported when monitoring urea and electrolytes, and having the kidney function level on the patient record, does not translate to appropriate prescribing in RKF (Primary care: Farag et al, 2014. Hospital: Quartorolo et al, 2007; Kalendar-Rich et al, 2011; Nielson et al, 2004). Without any other input, this does not provide any increased awareness of the need to apply a reduced kidney function level to prescribing.

Field et al (2009) in Canada already had creatinine clearance displayed when prescribing but there was still inappropriate prescribing. Their intervention was an alert triggered when a listed drug was ordered and CrCl-CG was <50 ml/min. Although significantly higher proportions of final drug orders were appropriate in the intervention units, the system did not improve the rate at which appropriate doses were ordered. This implies that not all the determinants for appropriate prescribing are being addressed for the prescribers, and might show a need for more education and training.

Ehrler et al (2009) describe an intervention of a workshop, desk-top checklist, patient information and dosing software for over 800 drugs aimed at prescribers. However, follow-up analysis revealed that the positive effect found was mostly related to ACEIs and ARBs which suggests a reduced usefulness for other drugs affected by kidney function. The dosing software provided was well received, but it could not integrate with the patient record system and so the prescriber needed to remember to use the system for affected drugs, which might be why few drugs were altered. Awareness only seems to have been raised for one group of medicines with this intervention.

Forough et al (2014) used a text alert system when CrCl was <50 ml/min and showed a benefit where doses needed alteration, but no benefit for drugs that needed stopping, again suggesting that not all the barriers of awareness and understanding had been addressed.

Many of the interventions described involved pharmacists recognising the need for drugs to be altered or reviewed and then flagging that up to the prescriber. The

interventions are reported as having a positive outcome, but the studies report that not all recommendations are accepted or followed through. For community pharmacist interventions to GPs, there was a 66% acceptance rate in the Joosten et al (2013) study, 50% reported by Geerts et al (2013), and only 33% accepted in the Via Sosa et al (2014) study. This was similar for pharmacists making recommendations for care home patients on drugs needing review because of RKF (Gheewala et al, 2014; Barnes et al, 2014). Awareness does not seem to have been increased for prescribers in these interventions, and an education element may have meant an increased understanding of the need for altering prescribing and acceptance of the pharmacist recommendation.

The GP interview study revealed a wide lack of awareness of the need to assess kidney function for many drugs, and the consensus group study showed that the doctors on the panel ranked 'increasing understanding' as a top 3 priority compared to the pharmacists, who ranked it lower. The doctors also all strongly agreed that the calculation of creatinine clearance should be easier in the prescribing process, whilst the pharmacists again ranked this lower. This suggests that pharmacists may overestimate GP understanding, and so may underestimate the need to include education and training in the intervention.

6.2.2 Patient and drug specific warnings/prompts are needed at medication review as well as initiation

Many studies showed that alerts were overridden and not acted upon (Cho et al, 2014; Youseff et al, 2015; Desmedt et al, 2012; Sellier et al, 2009). These alerts clearly did not address the needs of the prescriber, whether there was a need for education and training, the alerts were popping up at the wrong times, or maybe they were not patient and drug specific.

Frolich et al (2011) surveyed the effect of a computerised decision support system and found it generated a large number of alerts, with only a minor fraction likely to be of substantial risk to the patient. Czock et al (2015) showed that a non-specific alert system would yield an average number of alerts per medication regimen of 2.22, but by tailoring alerts to be patient and drug specific, the alert burden was reduced by 90%. Melton et al (2015) seemed to have previously tried using alerts but they had not been successful, and so they conducted a qualitative exercise to redesign their alerts. They found using the new alert there were 43% fewer prescribing errors compared with the original alerts. When laboratory links were presented on the redesigned alert,

laboratory information was accessed 3.5 times more frequently. Using a qualitative enquiry to explore the determinants significantly improved the usability of the alert.

No studies found explored interventions that addressed the need for assessing kidney function at medication review in the primary care system. The current research project has shown the importance of the need for warnings and prompts at medication review as kidney function can change, and is likely to reduce as a patients gets older, so a drug may have been appropriate when it was initiated, but it may not continue to be over time.

6.2.3 Kidney function assessment for older people should be a required part of the prescribing process

Most of the intervention studies found in the scoping literature review did not attempt to make changes to the prescribing process, or encourage the prescriber to think about kidney function as a routine. Many were alerts triggered by a drug being prescribed when kidney function was low, so the prescriber hadn't thought of it before choosing the drug or dose (for example, Forough et al, 2014). Other studies were also reacting to an 'error' made by the prescriber, such as the pharmacist intervention studies (for example, Geerts et al, 2012). These interventions rely on inappropriate prescribing being flagged up by a pharmacist or technology and then being accepted by the prescriber. The intervention has not addressed the causes of the original error, except maybe that there can be an educational element to the alert, or the pharmacist response.

By aiming to explore how to make kidney function assessment part of the prescribing process, this intervention priority is wanting to help prescribers to apply the recommendations where needed when prescribing, and not make an error that needs to be corrected.

6.2.4 A recent kidney function check needs to be available at medication review

As already mentioned, no studies were found that explored interventions addressing the need for assessing kidney function at medication review in the primary care system. Many drugs are taken by patients for a long time and changes in kidney function level need to be considered.

Using a systematic theory based method to explore the determinants has highlighted this important factor that has not been previously recognised or addressed.

6.2.5 Implication for the current research

The lack of theoretical underpinning in the intervention studies found in the scoping literature review might be a factor where there was little or no benefit found, and means that any positive effect is difficult to replicate and make sustainable. The current research has been able to target priorities for intervention to identified barriers, and so is more likely to lead to an intervention that addresses what needs to change to help prescribers apply the recommendations in RKF.

6.3 The research findings and intervention priorities with respect to current contexts when prescribing for older people in primary care

In all the stages of this research, it has been highlighted that older people are at increased risk of harm if prescribing recommendations are not applied, as they are more likely to have reduced kidney function, and also more likely to be taking multiple medications. The intervention priorities need to be considered as to how they might be developed into an intervention that encompasses, and works with, contextual drivers of behaviour relating to prescribing for older people, as well as with current national policies in the NHS.

6.3.1 Contextual drivers of behaviour relating to prescribing for older people

6.3.1.1 Medication review

There is a progressive loss of the functional capabilities of most body organs with increasing age, changes in responses to receptor stimulation, and a decrease in homeostatic mechanisms, which have implications for drug handling. Of these changes though, excretion is the most significant and important age-related pharmacokinetic change and is both predictable and measurable (Beers and Berkow, 2000; Grimley-Evans et al, 2000). Regular monitoring and review of medications therefore becomes more important with increased age. Two of the four intervention priorities focus on medication review, to have a recent kidney function check available at the review, and that the prompts and warnings available when initiating a drug

should be easily available at medication review. This was a key theme identified from the GP interview study that hadn't been identified previously as a problem, and had not been found in the scoping literature review. If an intervention can be developed to provide warnings when reviewing medications, it would have the added benefit of providing warnings for other recommendations such as liver function. If the recommendation for patient and drug specific warnings and prompts for kidney function level were possible, it could also be achieved for other tests which would make them more relevant and helpful for the prescriber.

Currently, GPs have limited time in a short consultation for medication review, and only very rarely are tools used to structure that review, such as a custom built template, or the 'NO TEARS' tool for medication review (Lewis, 2004). If a review tool could be developed to incorporate patient and drug specific warnings and prompts available, it could potentially help prescribers to highlight where to focus their time.

Pharmacists have been highlighted by the GP interviewees and the consensus group expert panel as healthcare professionals who could be part of the solution by doing medication reviews, and audit to highlight where review is needed. They were also highlighted as an educational resource. The PINCER study (Avery et al, 2012) showed that pharmacist-led feedback, educational outreach, and dedicated support is an effective method for reducing a range of medication errors in general practices with computerised clinical records, and other studies have shown the benefit of pharmacist medication review, for example Zermansky et al (2001) and Blenkinsop et al (2012).

6.3.1.2 Frailty

There are current initiatives to identify 'frailty' in patients which has been defined by the British Geriatrics Society (2014) as a distinctive health state related to the ageing process in which multiple body systems gradually lose their in-built reserves. They state that around 10% of people aged over 65 years have frailty, rising to between a quarter and a half of those aged over 85 years, and older people living with frailty are at risk of adverse outcomes such as dramatic changes in their physical and mental wellbeing after an apparently minor event which challenges their health, such as an infection or new medication.

The findings from this research project have shown that older people are more likely to have a lower kidney function, and so a lower reserve to react normally to assaults such as dehydration or nephrotoxicity by drugs.

Rockwood et al (2005) have described a model of frailty which assumes an accumulation of deficits which can occur with ageing and which combine to increase the 'frailty index' which in turn will increase the risk of an adverse outcome. They include multiple medications as a factor and that many drugs are particularly associated with adverse outcomes in frailty such as:

- Antimuscarinics in cognitive impairment.
- Long acting benzodiazepines.
- Some sulphonylureas.
- Other sedatives and hypnotics increase falls risk.
- Opiate based analgesics increase risk of confusion or delirium.
- NSAID can cause severe symptomatic renal impairment in frailty.

It should be noted that all the above drug groups mentioned by the authors have recommendations for reduced use when kidney function is low.

An 'Electronic Frailty Index' has recently been developed in the UK which aims to help identify and predict adverse outcomes for older patients in primary care (Clegg et al, 2016). This index is made up of 36 deficits which include one for CKD and one for polypharmacy. The findings from the current project would suggest that not all older people with a kidney function low enough to affect their prescribed medications would be picked up by a 'CKD' marker as that uses eGFR. There has also been much discussion around older people not necessarily having CKD when kidney function is reduced as there is a natural decline with age. The Frailty Index could potentially be improved by using CrCl-CG linked to drugs. The intervention priorities would aim to improve having a recent kidney function test available and to have that as CrCl-CG in the patient record to be available for prescribing decisions.

6.3.1.3 Multimorbidity and polypharmacy

Having more than one long-term health condition adds complexity to the management and care of patients, and the prevalence of long-term conditions is strongly linked to ageing (NICE NG22, 2015). There is a new NICE guideline just published, optimising care for people with 2 or more long-term health conditions (multimorbidity) by focusing on individual needs, preferences for treatments, and health priorities (NICE NG56, 2016). There is a section on medicines which discusses medication review and use of tools such as the 'STOPP/START' criteria which aim to screen older persons' prescriptions for potentially inappropriate drugs called STOPP (Screening Tool of Older Persons' Prescriptions) and criteria for potentially appropriate, indicated drugs called START (Screening Tool to Alert doctors to Right, i.e. appropriate, indicated

Treatment) (Gallagher et al, 2008). The STOPP criteria do include stopping NSAIDs where eGFR is 20-50ml/min, but no other criteria related to drug use and RKF, and the new NICE guideline does not include guidance on monitoring. This project has highlighted the importance of monitoring, and an intervention priority is to have a recent kidney function available for prescribing decisions.

Sinnott et al (2015) have stated that, despite the prevalence of multimorbidity, few interventions have been developed to improve medication management in this field. They discuss that multimorbidity affects over 60 % of patients in primary care, and that its association with polypharmacy makes the development of interventions to optimise medication management in patients with multimorbidity a priority.

Older people are more likely to be taking regular medications, with around 75% of those aged 60 years and older, and over 90% in the over 70s taking at least one prescribed medicine (Petty et al, 2014). The mean number of medicines per patient on repeat prescriptions is over 5 for the 60-69 year olds, and up to 7.1 for the over 80s (Petty et al, 2014). Multimorbidity means that older people are more likely to be taking multiple different kinds of drugs, and many drugs used for varying medical conditions are excreted by the kidney. The case-note review found 70 different drugs were prescribed when kidney function was reduced in the sample of older people from five GP practices, and the latest edition of the Renal Drug Handbook has over 800 drug monographs (Ashley and Dunleavy, 2014). The intervention priorities are that kidney function should be assessed and applied to all prescribing where appropriate, so an intervention will need to be able to help prescribers in the complexity of polypharmacy and multimorbidity.

Some groups of drugs have been highlighted for national scrutiny. For example GPs have been urged to review the use of anticholinergic medications in their elderly patients, particularly those with dementia, after researchers found their use was associated with declines in both physical and cognitive function in a systematic review (Fox et al, 2014). Declines in functioning were related to the number of anticholinergic drugs and length of time taken. What the authors did not consider in their report was that many anticholinergic medications are affected by kidney function and that many older people will have increased blood levels because of RKF, which could be a relevant factor.

The Kings Fund report on polypharmacy, the concurrent use of multiple medications by one individual, states that it is driven by the growth of an ageing population and the rising prevalence of multi-morbidity (Duerden et al, 2013). They define 'appropriate

polypharmacy' as extending life expectancy and improving quality of life, but medicines use has to be optimised and prescribed according to best evidence. In 'problematic polypharmacy' there can be an increased risk of drug interactions and adverse drug reactions, together with impaired adherence to medication and quality of life for patients. The intervention priorities would aim to promote 'appropriate polypharmacy' by aiming to ensure recommended drugs and doses are used in RKF. They will also help to stop drugs where they should not be used because kidney function is too low, reducing 'problematic polypharmacy'.

6.3.1.4 Deprescribing

As described in the Kings Fund report on polypharmacy (Duerden et al, 2013), where it is 'problematic', drugs should be optimised and stopped where appropriate. The process of reducing or discontinuing medications, with the goal of minimising inappropriate use and preventing adverse patient outcomes, is increasingly referred to as 'deprescribing' (Alldred, 2014). 'Deprescribing' is the process of withdrawal of an inappropriate medication, supervised by a health care professional with the goal of managing polypharmacy and improving outcomes' (Reeve et al, 2015). Although the term may be new, appropriate cessation or reduction of medication is a long accepted component of competent prescribing.

In the meta-synthesis by Anderson et al (2014) found in the scoping review, the authors showed that many factors were involved related to prescribers in stopping, or altering a medication a patient has been on for some time, which were highly interdependent and impacted by considerable clinical complexity. The themes broadly fell into awareness, inertia, self-efficacy and feasibility. They found that where there was polypharmacy, prescribers could not easily identify which medications were inappropriate. 'STOPP/START' mentioned in the previous section is an example of a recent tool developed to help prescribers identify drugs that should be stopped (Gallagher et al, 2008). If the intervention priorities identified can be developed into a useable intervention, it will help prescribers identify where kidney function is low and which drugs should be avoided, giving them the tools to encourage appropriate deprescribing.

6.3.1.5 Care homes medicines management

The 'CHUMS' study aimed to establish the prevalence, types and underlying causes of medication errors in care homes, estimate the ensuing harm and developing solutions to reduce the prevalence of error (Barber et al, 2009). They concluded that there is an

unacceptable prevalence of medication errors in care homes, affecting some of the most vulnerable members of society, and 'action is required from all concerned'. All the issues discussed previously around age related changes in drug handling, multimorbidity, polypharmacy, and deprescribing apply for people living in care homes.

Most reviews of patients in care homes are done by the practitioner visiting the home. An issue raised by the GP interviewees, and the expert panel, was that they do not have the electronic patient record when reviewing. The intervention priorities that aim to ensure a kidney function level is available when reviewing medicines, and to be a part of the prescribing process, would necessitate access to the patient record on home visits. Technologies are available to give mobile access to records that would need to be more widely available.

Studies found in the scoping literature review highlighted problems with medicines and RKF in care homes, and how pharmacists can improve prescribing by providing medication review with access to kidney function levels (Geewala et al, 2014; Barnes et al, 2014).

6.3.2 Contextual drivers of behaviour relating to current national policies in the NHS.

6.3.2.1 Reducing admissions

Reducing emergency admissions to hospital, both as a measure of care quality and to contain spiralling healthcare expenditure, is a notional priority. Emergency admissions in the United Kingdom rose by 47% from 1998 to 2013, from 3.6 million to 5.3 million, with only a 10% increase in population over this period. These admissions are expensive; in 2012 they cost the NHS £12.5bn. Wallace et al (2016) state that targeting specific conditions might reduce emergency admissions, and variation in medical practice should be considered. Many studies were found in the scoping literature review showing that not assessing kidney function in relation to prescribing can cause adverse effect and hospital admissions, for example Helldén et al (2009).

The intervention priorities would help prescribers identify where drugs should be altered, or doses reduced, to reduce the risk of harm and hospital admission.

6.3.2.2 Quality Outcomes Framework

The Quality Outcomes Framework (QOF) is the annual reward and incentive programme detailing GP practice achievement results. It rewards practices for the

provision of quality care and helps standardise improvement in the delivery of primary medical services, awarding practices achievement points for:

- Managing some of the most common chronic diseases, e.g. asthma, diabetes.
- Managing major public health concerns, e.g. smoking, obesity.
- Implementing preventative measures, e.g. regular blood pressure checks.

The 2006 QOF markers included formation of registers of patients with CKD stages 3, 4 and 5 as calculated by the MDRD equation. Although, since then there were further measures added including regular monitoring, the QOF marker is now back to just the formation of a register of CKD patients. Regular monitoring is no longer incentivised this way, and there has never been signposting to prescribing, or effect of RKF on prescribing.

At the time of the PCT-wide survey, there were QOF markers for medication review, but not currently:

'Medicines 11 A medication review is recorded in the notes in the preceding 15 months for all patients being prescribed 4 or more repeat medicines Standard 80%.'

'Medicines 12 A medication review is recorded in the notes in the preceding 15 months for all patients being prescribed repeat medicines Standard 80%.'

Currently there is no incentivisation through QOF for either medication review or for regular monitoring in CKD. The PCT-wide survey showed that it is feasible to collect the data required from the patient record system for kidney function level by CrCl-CG, and so it would be possible to set markers for safer prescribing that are encompassed in the intervention priorities. However, CrCl-CG is not often calculated currently, and is rarely read coded, which would make routine data collection more difficult. If the intervention priorities are developed into a usable intervention that means CrCl-CG is used routinely then it might be considered whether this method of incentivisation would help to reduce harm to patients from their medicines.

6.3.2.3 NICE guidelines

A recent systematic examination of recommendations in twelve NICE clinical guidelines concluded that drug-disease interactions with chronic kidney disease were common and that guideline developers should particularly consider whether chronic kidney disease is prevalent in the target population (Dumbreck et al, 2015). For example they state that prevalence of comorbidity with chronic kidney disease was about 14% in patients with type 2 diabetes, and 23% in patients with heart failure, so the implication might be that guideline developers should consider chronic kidney disease with heart failure, and possibly consider it with type 2 diabetes.

It has been previously discussed that the NICE CKD guidelines do not consider prescribing in RKF, other than for treatment, except to 'do a medication review'. This is also the case in other NICE guidance such as 'Managing medicines in care homes' guidelines (NICE SC1, 2014), long-term conditions guidance (NICE NG22, 2015), and multimorbidity guidance (NICE NG56, 2016).

The expert consensus panel stated that national guidance and quality standards act as a lever, and that they are transformative, providing a priority focus and leading to the teaching curriculum and national strategy such as use of QOF. They suggested that NICE guidance should be clearer on use of medications where parameters such as kidney function are not normal. There was also discussion by the panel on the intervention priorities, concluding that a NICE guideline on prescribing for older people would be useful, not only to give the latest evidence, but also to provide a lever and a focus for change and the education curriculum.

6.4 Intervention priorities – the next steps towards intervention development

The Behaviour Change Wheel (BCW) describes three broad stages: understanding the behaviour, identifying intervention options, and identifying content and implementation options. (Michie et al, 2014). These are subdivided into a further eight steps, the first four of which have been achieved in the research project so far:

BCW step 1: define the problem in behavioural terms.

BCW step 2: select the target behaviour.

BCW step 3: specify the target behaviour.

BCW step 4: identify what needs to change to achieve the desired behaviour.

The final four BCW steps were out with the time and scope of the PhD programme to undertake the additional studies. However, the intervention priorities defined by the consensus panel will direct the future ongoing stages of intervention development:

BCW step 5: identify intervention functions to achieve the desired behaviour.

BCW step 6: identify policy categories.

BCW step 7: identify behavioural change techniques.

BCW step 8: identify mode of delivery.

A systematic review of frameworks of behaviour change interventions identified 19 frameworks which comprised nine intervention functions and seven policy categories (Michie et al, 2011). The resulting Behaviour Change Wheel integrated framework links these intervention functions and policy categories to the COM-B model (Figure 33).

Potential intervention functions and policy categories identified by the Behaviour Change Wheel need to be considered for the intervention priorities agreed by the consensus panel, and these will then inform the selection of potential behaviour change techniques.

6.4.1 Intervention functions

The links between COM-B, TDF and intervention functions have been identified in a consensus exercise (Michie et al, 2014, pp113-115) and this has been used to indicate possible intervention functions to consider for the intervention priorities agreed by the consensus panel. Figure 35 show the priority TDF domains, and the potential intervention functions that might be considered for each intervention priority. The TDF domains are the five identified in the GP interview study linked to the four intervention priorities. Three further domains have been included:

- **Beliefs about consequences**, as patient safety was expressed to be an important motivation for prescribers.

- **Professional/ social role and identity**, as prescribing was described by GPs as a key role and they wanted to do it correctly. Also the finding that there was less responsibility for the prescribing felt when doing a medication review which should be an important consideration when developing an intervention.

- **Social influences**, as pharmacists were specifically identified as a group who should be considered.
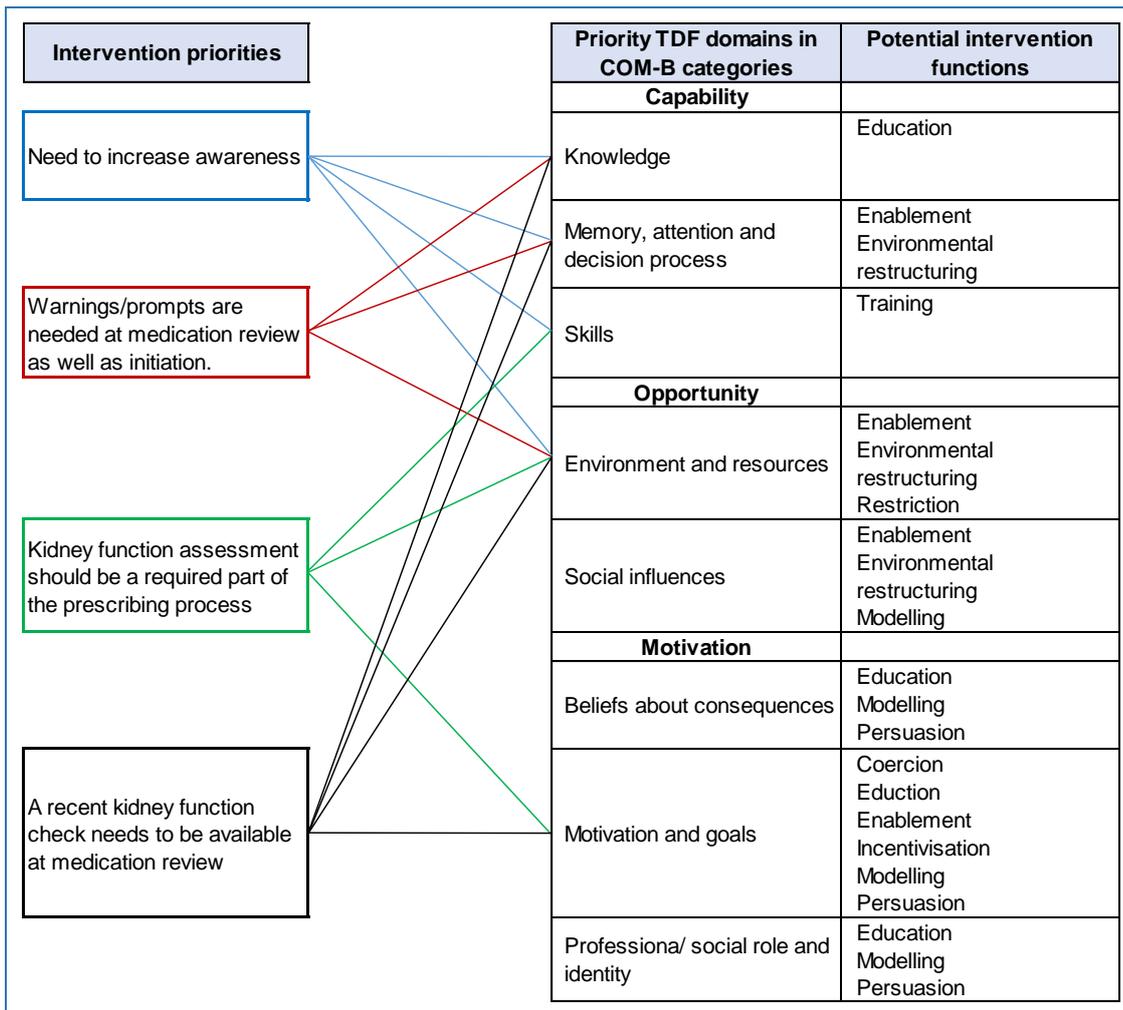
Figure 35: Potential intervention functions identified from the Behaviour Change Wheel (Michie et al, 2014)

All seven of the intervention functions are listed in Figure 35 for the relevant domains, but restriction and coercion would not be applicable. The other five intervention functions can be considered for a potential intervention:

- **Education**: increasing knowledge or understanding. Education will need to an important part of an intervention, as lack of knowledge about prescribing in RKF has emerged as a major theme. Suggestions from the GPs and expert panel have included education at all levels, in medical training, GP training, continued professional development, and specialist clinical areas. Technological solutions such as warnings or prompts can include educational elements, and educational outreach visits could be included. Strategies such

as 'audit and feedback' (Ivers et al, 2012) can be educational, as well as persuasive.

- **Training**: imparting skills. Prescribers need to know how to implement recommendations in the prescribing process, and how to access the required data on the patient record systems. Training could help prescribers to form personal rules, action plans, and to remember and apply recommendations.

- **Environmental restructuring**: changing the physical or social context. Technological solutions could be developed to make applying the recommendations easier in the prescribing process. Making warnings and prompts patient and drug specific would make them more useable, and making them easily available at medication review would be important. Pharmacists could be more involved with medication review and audit. Community pharmacists might have kidney function results to inform use of medicines.

- **Enablement**: increasing means/ reducing barriers to increase capability (beyond education and training) or opportunity (beyond environmental restructuring).

- **Modelling**: providing an example for people to aspire to or imitate. Case studies could be used to induce automatic imitation and change habit.

- **Persuasion**: using communication to induce positive or negative feelings or stimulate action. Respected leaders and peers could be used to persuade of the need to assess kidney function in the prescribing process. Pharmacists have been suggested as being respected in this area. GPs were motivated by not doing harm which can be used to persuade prescribers of the importance of applying recommendations.

- **Incentivisation**: creating an expectation of reward. The Quality Outcomes Framework has previously incentivised GP practices in care for patients with CKD including regular kidney function monitoring, but now it is only to keep a register. The data is available to provide reports and so kidney function as creatinine clearance could be reported if it was agreed to be prioritised this way.

The APEASE criteria (affordability, practicability, effectiveness/ cost-effectiveness, acceptability, side-effects/ safety, equity) for designing and evaluating interventions and intervention ideas will be used to select the most appropriate intervention functions (Michie et al, 2014).

6.4.2 Policy categories

The next step in developing an intervention strategy will be to consider what policies would support the delivery of the intervention functions. The 19 framework synthesis identified seven policy categories representing types of decisions made by authorities that help to support and enact the interventions. Fiscal measures, regulation, and legislation are not likely to be applicable, but potential policy categories that could be considered using the APEASE criteria are:

- **Communication/ marketing**: using print, electronic, telephonic or broadcast media.

- **Guidelines**: creating documents that recommend or mandate practice. This includes all changes to service provision.

- **Environmental/ social planning**: designing and/ or controlling the physical or social environment.

- **Service provision**: delivering a service.

6.4.3 Content and implementation options

The final stage in intervention development will be to identify content and implementation options i.e. which behaviour change techniques (BCTs) and the mode of delivery. A BCT is defined as 'an active component of an intervention designed to change behaviour', with defining characteristics that are observable, replicable, an irreducible component of an intervention designed to change behaviour and a postulated active ingredient within the intervention (Michie and Johnstone, 2013). It is the smallest component in the proposed mechanisms of change, and can be used alone or in combination with other BCTs. Behaviour specific taxonomies of BCTs have been synthesised and refined to produce a BCT taxonomy with 93 BCTs organised into 16 groupings (Michie et al, 2013). All BCTs that could be considered for any particular intervention function, guided by the definition, will be considered, and then narrowed down to those most likely to be appropriate. The modes of delivery will also need to be considered.

6.5 Strengths and limitations

These pragmatic studies using mixed methods have given a comprehensive picture of the extent of inappropriate prescribing in RKF, and what needs to change to help prescribers apply the prescribing recommendations. The application of several robust and reproducible research methods studying of the same problem area has given cross-verification, reducing the weaknesses and biases of single method studies. The investigation has been driven by the research questions, and derived from the integration of methods and results from the previous studies. It has combined data from both quantitative and qualitative methods to address the different research questions and enhance the validity of the findings. Updating of the scoping literature review led to a re-analysis of the prescribing data from the cross-sectional survey to include a 'cases missed' analysis, adding strength to the quantitative analysis, giving a clear measure of the impact for patients, as well as a comparison to the other studies in the literature.

The problem has been mapped, tested in a wide population, and explored to find what needs to change. There has been good participation and support from GP practices, interviewees and panellists throughout the project.

The project was based in one former PCT which is not a typical population with fewer older people than the England & Wales average, so the findings may be an underestimation of the problem in the UK. The GPs interviewed were from a small localised area, but there was a wide range of prescribing experience, clinical interests and specialities, and so the findings may be more likely to be applicable in a wider context. Primary care studies in France and Australia (Breton et al, 2011; Khanal et al, 2015) have also found a high prevalence of inappropriate prescribing for older people with RKF lending weight to the generalisability of the findings.

Patient and public involvement in the project was considered, but the initial key aim of this project was to investigate whether there was a problem of prescribing recommendations in RKF not being applied. Having established that there is a need for intervention, it is planned that there should be patient and public involvement in the planning and participation in the subsequent stages of research. The consensus panel raised the issue that patients do not tend to have any awareness of kidney function unless they have severe disease. Raising the issues of reduced kidney function in those who are unaware would need sensitive consideration.

As a single researcher, overseen by the supervision team, there was a vision and a consistency carried through the project. However, it may mean biases are introduced

to the methods and analysis. The reproducibility may be reduced by my professional involvement, which may have contributed to the rich data collected, but also could have meant an assumed shared language and understanding. Specialist expertise was sought to verify reliability, and there was an iterative process of reflection, as well as comparison with methods and results from similar studies from hospital and other countries, lending greater confidence in the conclusions.

6.6 What this project adds to the literature

No evidence was found in the literature on the prevalence of inappropriate prescribing for older people with RKF in UK primary care, or the determinants of prescriber behaviour in this area, suggesting that these studies are the first in the UK.

This project has added to the body of literature on:

- The international evidence base for prevalence of inappropriate prescribing for older people with RKF.
- The necessity of using the Cockcroft Gault equation with ideal body weight, or actual if lower, to estimate kidney function for prescribing decisions, particularly for older people.
- The UK evidence base for prescriber behaviour.
- The use of a scoping literature review, the TDF, and consensus group methods in healthcare research.

The focus for this research has been on older people. It has been previously highlighted that this age group are generally under-represented in medication related research (Avorn, 2010). Older people were not included in the kidney function estimation equation development studies and yet, in 2013, people aged 65 years and older took 60% of all dispensed medications in England & Wales (Health and Social Care Information Centre, 2014), emphasising the necessity of research focussed on this age group.

6.7 What this project adds to practice and policy

Highlighting the issues to both clinicians and policymakers is the first stage in minimising inappropriate prescribing in routine clinical practice. Further research is needed to ensure an intervention will be more likely to be successful in changing practice, and not have unintended consequences.

The impact of this project on practice and policy has already included:

Locally:

- Development of a guideline for the assessment of kidney function for use of new oral anticoagulants (NOACs) in the Bradford deep vein thrombosis (DVT) pathway, and in the anticoagulant clinics.

- Assessment of kidney function included in pharmacy team audits.

- Key prescribing performance indicators to review medications for people with chronic kidney disease.

Regionally:

- Involvement with the Yorkshire regional AKI forum: educational sessions, and resource development.

Nationally:

- The guideline for the assessment of kidney function for use of new oral anticoagulants (Wood et al, 2013) is being used widely, for example:
  - As part of a Primary Care DVT pathway in Horsham and Mid Sussex CCG.
  - To aid safe prescribing of NOACs in primary care in North Somerset CCG, Aylesbury Vale CCG, Chiltern CCG, Buckingham CCG, Bury and Greater Manchester.

- Participation on a diabetes advisory board resulting in the inclusion of a 'reducing risk of medicines in RKF' component on a data 'dashboard' for use in primary care.

The requirements for education and training need to be developed and implemented. The consensus panel agreed that a submission should be made to the BNF Formulary Committee to clarify the advice and information for prescribing in RKF, particularly in relation to prescribing for older people. Both the front 'prescribing in renal impairment' section and the individual drug monographs could be improved to help application of the prescribing recommendations. The panel also highlighted that the 'renal calculator' on at least one of the national GP patient record systems needs to be corrected to use the best evidence-based variables, and this has since been rectified.

Dumbreck et al (2015) have highlighted that guidelines need to consider recommendations for drug use in relation to level of kidney function. CKD and AKI guidelines could include guidance on prescribing to both reduce the risk to the kidney, and reduce ADRs from all renally excreted drugs. The NHS England 'Think Kidneys'

campaign resources include an 'AKI medicines optimisation toolkit' aimed at prescribers in hospitals (NHS England, 2015), but it could be usefully extended to primary care to help reduce the risk of AKI from drugs. The consensus panel also suggested that a new NICE guideline on prescribing for older people would be a focus for change and education.

Having the warnings and prompts at medication review would have the added benefit of highlighting other parameters that might need assessment, such as liver function and thyroid function tests.

6.8 Translation and impact

6.8.1 Publication and presentation

Publication:

- Wood, S., Petty, D., Glidewell, L., Raynor, T. 2011. Are we over-dosing our elderly patients with renally excreted drugs in primary care? International Journal of Pharmacy Practice, 19(suppl. 2), p.38.

Publications arising from issues raised in practice:

- Wood, S., Petty, D., Fay, M., Lewington, A. 2013. Assessing kidney function in oral anticoagulant prescribing: an aid for safer drug and dose choices. British Journal of Cardiology, 20, pp.61–64.

- Wood S. Anticoagulant dosing in reduced renal function for stroke and systemic embolism prevention in non-valvular AF. Guidelines in Practice 2013, (suppl).

- Howard, P. and Wood, S. 2013. Outcomes with the use of nitrofurantoin in renal impairment in primary care − a pilot study. European Journal of Hospital Pharmacy, 20, p.A114.

Poster presentations:

- The Royal Pharmaceutical Society Conference 2011.
- The Renal Association Conference 2012.
- The University of Leeds School of Healthcare Postgraduate Research Conference 2011 (first prize achieved).
- The University of Leeds School of Healthcare Postgraduate Research Conference 2014.

Oral presentations:

- The University of Leeds School of Healthcare Postgraduate Research Conference 2015.
- The Health Services Research & Pharmacy Practice Conference 2016.
- The International Social Pharmacy Workshop 2016.
- The Yorkshire Regional AKI Forum.
- Bradford primary care AKI/CKD education event.
- The Mixed Methods module group, University of Leeds School of Healthcare.

Plan for publication:

- 'A scoping literature review to identify the evidence base on prescribing for older people with reduced kidney function.'
- 'A cross-sectional survey of prescribing data to investigate whether recommendations for prescribing are applied for older people across a PCT population.'
- 'A qualitative GP interview study to explore why prescribers do not apply prescribing recommendations for older people with reduced kidney function.'
- 'A consensus group method to identify key themes for development of an intervention strategy and future research into prescribing for older people with reduced kidney function.'

6.8.2 Further research

The next stage of research will be an application for funding for a feasibility study before intervention implementation research, including patient and public involvement. Other questions have been raised during the process that might be possible to pursue in the future, such as 'does reducing the burden of drugs excreted by the kidney improve kidney function for older people with RKF?'

6.8.3 Impact for patients and the NHS

Implementation of better practice is likely to reduce the risk of harm from medications. Using recommended drugs and doses could also mean that older people can continue to use beneficial treatments that might have been stopped if doses were too high and caused ADRs.

ADRs, and harm related to medicine given during inpatient stays, have been estimated to cost £770m in 2007 in England, and that £5m was spent on litigation for drug-related medical errors between 1995 and 2007 (Frontier Economics, 2014). Helldén et al (2009) found a third of admissions for older people with ADRs were caused by RKF suggesting a high financial impact.

6.8.4 Impact for myself

This process has enabled me to become more confident about the evidence around prescribing in RKF, and presentation of the issues. The skills gained have also impacted on my professional life by:

- Questioning the status quo more.

- Having the confidence and skills to pursue clinical, professional and research problems.

- Awareness of the need to explore the wider aspects of behaviour change, such as systems, habit or emotion, when questioning issues in prescribing.

As a pharmacist, reducing risk from drugs is my ultimate aim.

6.9 Conclusion

At least 40% of all people aged 65 years and older are prescribed drugs that are excreted by the kidney and which have recommendations for altered use when kidney function is reduced. Older people are more likely to have RKF, but, although eGFR is routinely reported by pathology, and most have a recent kidney function estimate on their record, it is not applied to prescribing decisions by GPs. When looking at specific renally excreted drugs, 10.1% of ≥65 year olds, and 39.5% of ≥85 year olds, had a kidney function too low for the medication, or dose, they were prescribed, increasing the risk of ADR, harm and hospitalisation. Evidence of actual harm was found when reviewing case-notes.

This research has mapped and highlighted the prevalence of inappropriate prescribing in RKF in primary care and explored the behaviour determinants. It has identified what needs to change in practice and policy, and what further research is required, to improve patient safety.

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8   Appendices

8.1   Appendix 1: case-note review patient details form

Practice..................................... Pt Number................... M/F……… Age………

diabetic?..................other current problems……………………………………

eGFR ……………………   CKD stage   ………………..   date …………..

CrCl calculated by Cockcroft & Gault <u>(140-age) x IBW</u> (x1.2 if male) =

Serum creatinine   ....

Potentially nephrotoxic drugs

Drug	recommendation	Comment

Other renally cleared drugs

Drug	recommendation	Comment

Other drugs

Other comments

Pharmacist…………………………………   date………………

8.2 Appendix 2: the 70 different drugs encountered in the case-note review not used according to recommendations in RKF with patient numbers and BNF/SPC recommendations.

drug	number of pts where drug is not being prescribed as recommended at their CrClCG level	number of pts where drug may not be being prescribed as recommended at their CrClCG level and need review	number with eGFR 30-59	number with eGFR <30	BNF recommendation	additional SPC information
simvastatin	52		43	9	doses above 10mg with caution if <30ml/min	
alendronic acid	24		19	5	avoid if CrCl<35ml/min	terminal half-life > 10 years; any not deposited in the bone is rapidly excreted via the kidneys.
bendroflumethiazide	24		21	3	ineffective at <30ml/min	The dosage of thiazide diuretics may need to be reduced in the elderly, particularly when renal function is impaired, because of the possibility of electrolyte imbalance.
Calcichew D3 forte	10			10	NICE - colecalciferol ineffective in CKD stg 4 & 5 - need to change to alfacalcidol	
allopurinol 300mg	8		5	3	max 100mg daily	300mg in CrCl of10-20ml/min resulted in plasma conc expected from 600mg dose.
rosuvastatin	8		6	2	do not exceed 20mg if 30-60ml/min avoid if <30ml/min	
atenolol 100mg	7		5	1	15-35 - max 50mg <15 - max 25mg od or 50mg alt days	
chlortalidone	5		5		ineffective at <30ml/min	
indapamide	5		5		ineffective at <30ml/min	containdicated at <30ml/min; only fully effective if renal function is normal or only minimally impaired
lercanidipine	5		2	3	avoid if <30ml/min	
ranitidine	5		4	1	use 1/2 dose if <50ml/min	
ibuprofen gel	4		4		use lowest effective dose for the shortest possible duration; monitor for renal function, sodium and water retention. Deterioration reported after topical use	
lisinopril	3	6	5	4	use with caution and monitor response; hyperkalaemia and other s/es more common	CrCl 30-80ml/min - AUC increased by 13% CrCl 5-30ml/min - AUC x4.5 normal
baclofen	2		2		use smaller doses e.g. 5mg od	eliminated largely unchanged in the kidneys. Signs of overdose have been observed in pts with renal imp taking more than 5mg; particular caution with drugs that can affect renal function
digoxin	2	1	3		reduce dose; toxicity increased by electrolyte disturbance.	impaired renal function and low lean body mass in the elderly influences the pharmacokinetic of Lanoxin such that high serum digoxin levels and associated toxicity can occur quite readily
escitalopram	2		2		caution if <30ml/min	eliminated more slowly in elderly patients compared to younger patients. Systemic exposure (AUC) is about 50% higher in elderly compared to young healthy volunteers

ibuprofen	2		2		use lowest effective dose for the shortest possible duration; monitor for renal function, sodium and water retention	
metformin	2	11	11	2	NICE - review if <45ml/min and avoid if <30ml/min	CI'd if CrCl <60ml/min
moxonidine	2		1	1	max 400mcg od if 30-60ml/min and avoid if <30	
ramipril	2	16	16	2	use with caution and monitor response; hyperkalaemia and other s/es more common	ramipril is entirely metabolised; the metabolites are mainly renally excreted including the active ramiprilat.
strontium	2		2		avoid if <30ml/min	
anastrazole	1			1	avoid if CrCl <20ml/min	
atenolol 50mg	1			1	15-35 - max 50mg<15 - max 25mg od or 50mg alt days	
bezafibrate	1		1		reduce dose to 400mg od if 40-60ml/min, 200mg if 15-40, avoid if <15	elimination is markedly slowed in the presence of limited renal function
candesartan	1	9	9	1	initial dose 4mg	In the elderly (over 65 years) C_{max} and AUC of candesartan are increased by approximately 50% and 80%
ciprofibrate	1		1		reduce to 100mg on alt days in mod renal failure and avoid in severe.	Impaired renal function may increase the risk of myopathy.
colchicine	1			1	reduce dose at <50ml/min and avoid at <10ml/min	to be given with great care in the elderly due to cumulative toxicity.
diclofenac gel	1	1	2		use lowest effective dose for the shortest possible duration; monitor for renal function, sodium and water retention. Deterioration reported after topical use	
domperidone	1			1	reduce dose	contraindicated in renal impairment; $t_{1/2}$ is prolonged
eplenerone	1			1	incr risk of hyperkalaemia; avoid if <50ml/min	Periodic monitoring of serum potassium is recommended; CI'd if CrCl <50ml/min
fenofibrate	1		1		134mg if <60ml/min; 67mg if <20ml/min, avoid if <15	
gabapentin	1		1		reduce the dose - consult the product literature	>80ml/min - total dose mg/day: 900 - 3600mg 50-79 600 - 1800mg 30-49 300 - 900mg 15-29 300 - 600mg alt days <15 - reduce further in proportion to CrCl
hydrochlorthiazide	1			1	ineffective at <30ml/min	
hydroxyzine	1		1		use half normal dose	
ibandronic acid	1		1		avoid if <30ml/min	
irbesartan	1	2	1	2	use with caution and monitor response; hyperkalaemia and other s/es more common	
nitrofurantoin	1		1		avoid if <60ml/min	is contra-indicated in patients suffering from renal dysfunction with a creatinine clearance of less than 60ml/minute or elevated serum creatinine (chronic pulmonary reactions are more common in elderly)

olmesartan		1		1	max 20mg if 20-60ml/min; avoid if <20	
pantoprazole		1	1		max oral dose 40mg	
primidone		1	1		use with caution	
propranolol		1	1		caution - dose reduction may be required	
quinapril		1	1		use with caution and monitor response; hyperkalaemia and other s/es more common	(GFR 30-60 ml/min), AUC increased by 85% and clearance decreased to 52%.
sertraline		1	1		manufacturer advises caution	
tramadol		1		1	reduce dose of opioids - incr and prolonged effect, incr cerebral sensitivity	
total 70	201	107	231	77		

Appendix 3: literature search term categories

#NAME?	Subject heading	keywords ('OR')
Adverse Drug Reactions - ADR	Drug toxicity explode Medication errors	(drug adj2 (problem* or event* or error* or adverse)) (adverse adj3 (reaction* or event*)) ADR (medication adj2 (error* or safety or adverse)) (renal risk adj (drug* or medication*)) nephrotoxic Hospital admission* Hospitali*
Decision support tools - DS	Decision Support Systems, Clinical Decision Making, Computer-Assisted Therapy, Computer-Assisted Decision Support Techniques	alert* drug dos* service dos* guid* (compute* adj3 (support or tool* or service*)) (decision adj3 (support or tool* or service*))
Elderly - E	Aged explode	elder* over 65* old* person* old* patient*
Guidelines/ recommendations - GR	guideline or practice guideline guideline adherence	guideline* guidance guideance recommendation* ((guid* or recommendation*) adj4 (adher* or comply or complia* or complie* or follow* or observ*))
Kidney function Equations/ diagnostic tests - KFT	Kidney Function Tests explode	(kidney adj4 (test* or check* or formula* or equation*)) Glomerular filtration rate GFR eGFR MDRD Cockcroft adj Gault Cockcroft-Gault

Prescribers - P	Physicians explode	prescriber* doctor* GP* general practitioner* MD* physician* phycisian*
Prescriber Behaviour - PB		((prescrib* or MD* or physician* or GP* or general practitioner* or doctor*) adj (behavi* or performance or error)) ((prescrib* or MD* or physician* or GP* or general practitioner* or doctor*) adj4 (knowledge or attitude* or belief* or barrier* or adhere* or implement* or compli*))
Prescribing - Pg	Drug Therapy explode Drug Prescriptions explode	prescrip* prescrib* 'drug use' 'medication use' drug dos* medication dos* medication order* dos* adjustment
Primary Care - PC	Primary Health Care general practice or family practice	(primary adj (healthcare or health care or care)) general practice GP*
Renal impairment - RI	Renal Insufficiency or renal insufficiency, chronic	(renal adj (impairment or failure or dysfunction or insufficiency)) (impaired adj (renal function or kidney function)) (reduced adj (renal function or kidney function or GFR or glomerular filtration rate or eGFR or creatinine clearance)) (kidney adj (failure or dysfunction)) (poor adj (renal function or kidney function)) (chronic adj (renal failure or kidney disease)) CKD eGFR decline
Additions	English only Reviews only	

8.3 Appendix 4: Medline search strategy for the literature review key review area 4

Medline

1. exp Physicians/

2. prescriber*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

3. doctor*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

4. GP*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

5. general practitioner*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

6. MD*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

7. physician*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

8. phycisian*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier][1]

9. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8

10. Guideline Adherence/ or Guideline/ or Practice Guideline/

11. guideline*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

12. guidance.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

13. guideance.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier][2]

14. recommendation*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

15. ((guid* or recommendation*) adj4 (adher* or comply or complia* or complie* or follow* or observ*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

16. 10 or 11 or 12 or 13 or 14 or 15

17. exp Drug Therapy/

18. exp Drug Prescriptions/

19. prescrip*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

20. prescrib*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

21. 'drug use'.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

22. 'medication use'.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

23. drug dos*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

24. medication dos*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

25. medication order*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

26. dos* adjustment.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

27. 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26

28. ((prescrib* or MD* or physician* or GP* or general practitioner* or doctor*) adj (behavi* or performance or error)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

29. ((prescrib* or MD* or physician* or GP* or general practitioner* or doctor*) adj4 (knowledge or attitude* or belief* or barrier* or adhere* or implement* or compli*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

30. 28 or 29

31. exp Kidney Function Tests/

32. (kidney adj4 (test* or check* or formula* or equation*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

33. Glomerular filtration rate.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

34. GFR.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

35. eGFR.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

36. MDRD.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

37. (Cockcroft adj Gault).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
38. Cockcroft-Gault.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
39. 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38
40. Primary Health Care/
41. Family Practice/ or General Practice/
42. (primary adj (healthcare or health care or care)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
43. general practice.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
44. GP*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
45. 40 or 41 or 42 or 43 or 44
46. 9 and 16 and 27 and 30 and 39 and 45
47. limit 46 to english language
48. 9 and 16 and 27 and 30 and 39
49. limit 48 to english language
50. 9 and 16 and 27 and 30
51. limit 50 to english language
52. limit 51 to ("review articles" and "qualitative (best balance of sensitivity and specificity)")

Footnotes:
1. 'phycisian' has been deliberately added in search term 8, as well as the correctly spelt 'physician' in term 7. The University of Leeds Library adviser suggested that as this term is frequently mis-spelt, it can increase the number of studies found.
2. 'guideance' has been deliberately added in search term 13, as well as the correctly spelt 'guidance' in term 12, on the advice of the University of Leeds Library adviser as in footnote 1.

8.4 Appendix 5: letter of access for the PCT-wide prescribing survey (Chapter 3)

NHS
Bradford and Airedale

NHS Bradford and Airedale
Research Management and Governance Support Team
Clinical Quality
Level 2
Douglas Mill, Bowling Old Lane
Bradford, BD5 7JR

Susan Wood
39 Emmott Dr
Rawdon
Leeds LS19 6RE

Date: 21st October 2011

Dear Susan,

Letter of access for your project : To what extent are recommendations for prescribing of renally excreted drugs implemented for the elderly in primary care?

This letter confirms your right of access to conduct research through NHS Bradford and Airedale for the purpose and on the terms and conditions set out below. This right of access commences on 21st October 2011 and ends on 31st March 2013 unless terminated earlier in accordance with the clauses below.

You have a right of access to conduct your project as confirmed in writing in the letter of permission for your study from this NHS organisation. Please note that you cannot start the project until after you have received the letter from us giving permission to conduct the project.

The information supplied about your role in projects at NHS Bradford and Airedale has been reviewed and you do not require an honorary research contract with this NHS organisation. We are satisfied that such pre-engagement checks as we consider necessary have been carried out.

You are considered to be a legal visitor to NHS Bradford and Airedale premises. You are not entitled to any form of payment or access to other benefits provided by this NHS organisation to employees and this letter does not give rise to any other relationship between you and this NHS organisation, in particular that of an employee.

While undertaking research through NHS Bradford and Airedale, you will remain accountable to Professor Theo Raynor at the University of Leeds. In addition you are required to follow the reasonable instructions of Mr Paul Carder, Research and Innovation Coordinator, in this NHS organisation or those given on his behalf in relation to the terms of this right of access.

Where any third party claim is made, whether or not legal proceedings are issued, arising out of or in connection with your right of access, you are required to co-operate fully with any investigation by this NHS organisation in connection with any such claim and to give all such assistance as may reasonably be required regarding the conduct of any legal proceedings.

You must act in accordance with NHS Bradford and Airedale policies and procedures, which are available to you upon request, and the Research Governance Framework 2005. You are required to co-operate with NHS Bradford and Airedale in discharging its duties under the Health and Safety at Work etc Act 1974 and other health and safety legislation and to take reasonable care for the health and safety of yourself and others while on NHS Bradford and Airedale premises. You must observe the same standards of care and propriety in dealing with patients, staff, visitors, equipment and premises as is expected of any other contract holder and you must act appropriately, responsibly and professionally at all times.

You are required to ensure that all information regarding staff remains secure and strictly confidential at all times. You must ensure that you understand and comply with the requirements of the NHS Confidentiality Code of Practice and the Data Protection Act 1998. Your right of access in this matter is strictly limited to staff data only as you will not be participating in any form of research involving patients.

http://www.dh.gov.uk/assetRoot/04/06/92/54/04069254.pdf

Furthermore you should be aware that under the Act, unauthorised disclosure of information is an offence and such disclosures may lead to prosecution.

You should ensure that, where you are issued with an identity or security card, a bleep number, email or library account, keys or protective clothing, these are returned upon termination of this arrangement. Please also ensure that while on the premises you wear your ID badge at all times if one is issued to you, or you are able to prove your identity if challenged. Please note that this NHS organisation accepts no responsibility for damage to or loss of personal property.

We may terminate your right to attend at any time either by giving seven days' written notice to you or immediately without any notice if you are in breach of any of the terms or conditions described in this letter or if you commit any act that we reasonably consider to amount to serious misconduct or to be disruptive and/or prejudicial to the interests

and/or business of this NHS organisation or if you are convicted of any criminal offence. Your substantive employer is responsible for your conduct during this research project and may in the circumstances described above instigate disciplinary action against you. NHS Bradford and Airedale will not indemnify you against any liability incurred as a result of any breach of confidentiality or breach of the Data Protection Act 1998. Any breach of the Data Protection Act 1998 may result in legal action against you and/or your substantive employer.

If your current role or involvement in research changes, or any of the information provided in your Research Passport changes, you must inform your employer through their normal procedures. You must also inform your nominated manager in this NHS organisation.

Yours sincerely,

Paul Carder
Research and Innovation Coordinator
NHS Bradford and Airedale

8.5 Appendix 6: email reply from the National Research Ethics Service re PCT-wide prescribing survey 4/12/2011 (Chapter 3)

Thank you for your further email enquiry. As you are aware, our leaflet "Defining Research", explains how we differentiate research from other activities, and is published at: http://www.nres.npsa.nhs.uk/applications/is-your-project-research/. Based on the additional information you have provided, our advice is that the project is not considered to be research according to this guidance and therefore does not require ethical review by an NHS Research Ethics Committee.

If you are undertaking the project within the NHS, you should check with the relevant NHS care organisation(s) what other review arrangements or sources of advice apply to projects of this type. Guidance may also be available from the clinical governance office.

Although ethical review by an NHS REC is not necessary in this case, all types of study involving human participants should be conducted in accordance with basic ethical principles, such as informed consent and respect for the confidentiality of participants. Also, in processing identifiable data there are legal requirements under the Data Protection Act 2000. When undertaking an audit or service/therapy evaluation, the investigator and his/her team are responsible for considering the ethics of their project with advice from within their organisation.

This response should not be interpreted as giving a form of ethical approval or any endorsement to your project, but it may be provided to a journal or other body as evidence that ethical approval is not required under NHS research governance arrangements.

However, if you, your sponsor/funder or any NHS organisation feel that the project should be managed as research, and/or that ethical review by an NHS REC is essential, then please write setting out your reasons and we will be pleased to consider your request further.

Where NHS organisations have clarified that a project is not to be managed as research, the Research Governance Framework states that it should not be presented as research within the NHS.

Regards
Queries Line
National Research Ethics Service
National Patient Safety Agency
4-8 Maple Street
London
W1T 5HD

Website: www.nres.npsa.nhs.uk
Email: queries@nres.npsa.nhs.uk

Ref: 04/31

8.6 Appendix 7: participant invitation letter for the GP interview study (Chapter 4).

Leeds School of Healthcare
Leeds Institute of Health Sciences
Faculty of Medicine and Health

Baines Wing
University of Leeds
Leeds LS2 9JT

UNIVERSITY OF LEEDS

Su Wood

Phone: 07866837665
e-mail: hcs9s4w@leeds.ac.uk

Version 2, 8/8/2013

8th August 2013

Insert name
Insert address

Dear Insert name of patient/professional

An exploration into prescribing for the older patient with reduced kidney function

I am writing ask for your help with this research project. I am a pharmacist currently working in Bradford District Clinical Commissioning Group practices as well as doing a PhD at the University of Leeds School of Healthcare in partnership with the Academic Unit of Primary Care. A practice audit and PCT-wide survey have suggested that recommendations for use and dosing of drugs for older patients with reduced kidney function are not often applied and we are hoping that the ultimate outcome of this project will be to help practitioners with this area of prescribing.

This project will explore general practitioners' experience in prescribing for older patients with reduced kidney function. I wish to talk to you about your experience, perspective and views on this subject with the aim of understanding the range of GP experience in primary care. Further information on the project can be found in the accompanying 'Participant Information Sheet'.

The interview will be confidential, aim to last 30 – 40 minutes and be planned to fit around your schedule at a place convenient to yourself. A certificate of attendance at interview will be given for CPD.

This study has been reviewed and approved by the University of Leeds School of Healthcare Research Ethics Committee (Approval number SHREC/RP/346) and WSYBCSU assurance (Ref:001_05_11_13_0000). If you would like any additional information please contact Su Wood (mob:07866837665).

Once you have completed the attached consent form, all you have to do is return it in the **FREEPOST** envelope provided. All expressions of interest sent back will go into a draw for an Amazon voucher in recognition of your time given. Please return the slip if you do not wish to be approached for interview so that I do not contact you again.

Many thanks for your time.

Yours sincerely

Su Wood   **On behalf of the research team**
PhD student

8.7 Appendix 8: participant consent form for the GP interview study (Chapter 4)

Leeds School of Healthcare
Leeds Institute of Health Sciences
Faculty of Medicine and Health

Baines Wing
University of Leeds
Leeds LS2 9JT

UNIVERSITY OF LEEDS

Participant Consent Form
Vs3 8/8/13

Name of Centre: School of Healthcare and Academic Unit of Primary Care, University of Leeds

Title of Study: An exploration into prescribing for the older patient with reduced kidney function

	Please confirm agreement to the statements by putting your initials in the box below
I have read and understood the participant information sheet	
I have had the opportunity to ask questions and discuss this study	
I have received satisfactory answers to all of my questions	
I have received enough information about the study	
I understand that I am free to withdraw from the study at any time without having to give a reason; however, I will not be able to withdraw any data two weeks after the interview because it will have been anonymised and analysed.	
I understand that my interview will be audio-recorded.	
I understand that any information I provide, including personal details, will be kept confidential, stored securely and only accessed by those carrying out the study.	
I understand that any information I give may be included in published documents but all information will be anonymised.	
I understand that findings from this study will be used to inform development of an intervention that is likely to be useable, feasible and effective to help make it easier to apply recommendations on drug and dosing in reduced kidney function.	
I agree to take part in this study	

Participant Signature	Date
Name of Participant	
Researcher Signature	Date
Name of Researcher	

Thank you for agreeing to take part in this study.

8.8   Appendix 9: participant information sheet for the GP interview study (Chapter 4)

Leeds School of Healthcare
Leeds Institute of Health Sciences
Faculty of Medicine and Health

Baines Wing
University of Leeds
Leeds LS2 9JT

UNIVERSITY OF LEEDS

General Practitioner Participant Information Sheet

An exploration into prescribing for the older patient with reduced kidney function.

Version 3 Date: 8/8/2013

You are being invited to take part in a research study. Before you decide, it is important for you to understand why the research is being done and what it will involve if you decide to take part. Please take the time to read the following information carefully and discuss it with others if you wish. Ask Su Wood (details below) if there is anything that is not clear or if you would like more information. Thank you for taking the time to read this.

What is the research about?
This study aims to understand your experience of prescribing for older patients with reduced kidney function. Findings from this study will be used to inform development of an intervention that is likely to be useable, feasible and effective to help make it easier to apply recommendations on drug and dosing in reduced kidney function.

Who is doing this study?
Su Wood, the principal investigator, is doing this study as part of a PhD research project with help from a team of researchers at Leeds University. Su Wood will be conducting the interview.

Why have I been asked to participate?
You have been identified as a General Practitioner working in primary care in Bradford or Leeds CCGs who will have prescribed for older patients.

Do I have to take part?
No. If you do not want to take part you do not have to. You do not have to give a reason.

What will be involved if I take part in this study?
If you decide to take part, we would like to talk to you about your views on prescribing for older patients with reduced kidney function (RKF). For example, your personal experience, how you feel about prescribing in RKF, and what makes it easier or more difficult. You will be invited to talk to a researcher for 30-40 minutes. This will take place at a time and place convenient to you. With your prior agreement the interview will be audio-recorded.

What are the advantages and disadvantages of taking part?

By taking part in this research we will understand more about the personal experience of prescribing for older patients with RKF. Findings from this study will be used to inform development of an intervention that is likely to be useable, feasible and effective to help make it easier to apply recommendations on drug and dosing in reduced kidney function.

All expressions of interest sent back will go into a draw for an Amazon voucher in recognition of time given. A certificate of attendance at interview will be given for CPD.

We do not think that taking part in the discussion will cause any disadvantages to you apart from taking your time. We appreciate that healthcare professionals have a very busy schedule and hope to minimise disruption by holding the interview at a time to suit you.

Can I withdraw from the study at any time?

You will be able to withdraw from the study at any time without giving a reason. However, you will not be able to withdraw any data two weeks after the interview because it will have been anonymised and analysed.

Will the information I give be kept confidential?

Yes, all information that identifies you will be strictly confidential and held securely at the University of Leeds; data handling procedures will be in accordance with the Data Protection Act 1998.

The audio recordings of the interview will be transcribed and the transcriptions will be anonymised so they will not identify you unless you state that you wish to be identified. The audio recordings will be destroyed once they have been transcribed and anonymised. The anonymous information will be stored securely. All other personal information e.g. names or numbers that could identify you will be kept separately in a secure location at the University of Leeds.

What will happen to the results of the study?

The results of the study will be presented and published. You will receive a summary of our findings. It will not be possible to identify you or your practice from any reports about the project.

Who has reviewed this study?

All research in the NHS is looked at by Research Ethics Committees to protect your interests. Ethical approval has been granted by the School of Healthcare Research Ethics Committee:-
Project reference number:
Date:

If you agree to take part, would like more information or have any questions or concerns about the study please contact Su Wood by phone on 07866837665 or email (hcs9s4w@leeds.ac.uk)

Lead supervisor: Prof D. K. Raynor email: D.K.Raynor@leeds.ac.uk telephone: 0113 343 1442

Thank you for taking the time to read this information sheet.

8.9 Appendix 10: certificate of attendance for the GP interview study (Chapter 4)

Leeds School of Healthcare
Leeds Institute of Health Sciences
Faculty of Medicine and Health

Baines Wing
University of Leeds
Leeds LS2 9JT

UNIVERSITY OF LEEDS

Certificate of attendance

Research study: An exploration into prescribing for the older patient with reduced kidney function

.... participated in a discussion on:

- The use and dosing of drugs for older people with reduced kidney function.

- The findings of the research study so far.

- Ideas to inform development of an intervention that is likely to be useable, feasible and effective to help make it easier to apply recommendations on drug and dosing in reduced kidney function.

Pre-reading and discussion = 1 hour

Signed... Date...............................

Su Wood PhD study November 2013

8.10 Appendix 11: participant pre-interview reading for the GP interview study (Chapter 4)

Pre discussion reading

Thank you very much for agreeing to discuss your experience and views on drug use and prescribing for older patients with reduced kidney function (RKF). If you could possibly read the following now, it might help you to think about the subject before our discussion.

In a case note study in 5 GP practices in Bradford[1] 25% of all patients aged 65 years or older were on a drug that needed stopping or the dose reducing because of their level of kidney function based on the recommendations given in the drug licence (Summary of Product Characteristics[2] - SPC). The study highlighted four main categories:

- Drugs to avoid at specified reduced levels of kidney function e.g. metformin, alendronic acid.

- Drugs that need reduced dosing e.g. gabapentin, pregabalin, simvastatin, ramipril.

- Drugs that are ineffective at reduced levels of kidney function e.g. nitrofurantoin, thiazides.

- Drugs that do not have specific recommendations other than 'caution' but are well known to be problematic in reduced kidney function (RKF e.g. NSAIDs, ACEIs, ARBs.

A cross-sectional survey of the PCT-wide prescribing database corroborated the practice level findings suggesting that recommendations for prescribing for patients with RKF are often not followed. For example, 73% of nitrofurantoin prescribed for patients aged 65 years and older was at a kidney function too low for an adequate urine concentration for effectiveness.

A pilot study[3] in a Bradford GP practice showed that patients with a reduced kidney function given nitrofurantoin were more likely to need further antibiotic treatment and a recent MHRA Drug Safety Update has highlighted this problem[4].

Thank you for taking time to read this and I shall look forward to discussing the issues around prescribing for older patients with RKF.

References
1. Wood SI, Petty D, Glidewell L, Raynor T. Are we over-dosing our elderly patients with renally excreted drugs in primary care? IJPP 2011;19 (suppl. 2):38
2. Summary of Product Characteristics. www.medicines.org.uk
3. Howard P and Wood S. Outcomes with the use of nitrofurantoin in renal impairment in primary care − a pilot study. Eur J Hosp Pharm 2013 20: A114
4. Nitrofurantoin: reminder on precautions for use, especially renal impairment in (elderly) patients. Drug Safety Update August 2013

8.11 Appendix 12: the topic guide for the GP interview study (Chapter 4)

Leeds School of Healthcare
Leeds Institute of Health Sciences
Faculty of Medicine and Health

Baines Wing
University of Leeds
Leeds LS2 9JT

UNIVERSITY OF LEEDS

Interview topic guide for semi-structured elicitation interviews

Version 2, 15/05/2013

Participant number

Introduction	*Introduction to subject: As I hope you gathered for the information sheet, I am doing this study as part of my PhD project and I am interested in your views on prescribing for older patients with reduced kidney function (RKF).* *Have you had a chance to read the summary of the findings from this project so far?* *What are your initial thoughts? Is this an area of prescribing you are aware of?*	
Construct domain	Interview questions	
Knowledge	We have talked about some of the evidence, I would like to find out about your knowledge and use of guidelines and resources. • What knowledge to you have about prescribing for older patients with RKF? Do you know what the effects might be of not following the recommendations? • Is this something that was part of your training on use of drugs? • Do you use any guidelines or resources? • How do you use resources (what do you physically do?) • What other evidence are you aware of?	
Memory, attention and decision processes	What thought processes might guide your decision to think about level of kidney function? • Is being aware of level of kidney function when prescribing for a patient something you would usually do? • In what situations, if any, might make you think of level of RKF in relation to prescribing?	
Skills	How easy or difficult is it to implement the recommendations available? What do you think are the skills are required to do this?	
Beliefs about capabilities	How confident are you about doing this? • What problems/difficulties do you think you might encounter in managing a patient... • What would help you overcome these problems/difficulties?	
Motivation and goals	How important do you feel it is to alter use of drug or doses according to level of kidney function? (in relation to other behaviours required to treat the patient).	

G:\uni\GP interviews PB in RKF\Topic guide Su Wood PB in RKF Vs2 June 2013.docxG:\uni\GP interviews PB in RKF\Topic guide Su Wood PB in RKF Vs2 June 2013.docx

Beliefs about consequences	What do you think are the benefits of implementing recommendations?
	• To self,
	   patients (what harms might be avoided?),
	   colleagues,
	   NHS – positive and negative,
	   long or short term,
	   financial.
	What do you think are the disadvantages?
	• To self,
	• patients (what harms might there be?),
	• colleagues,
	• NHS – positive and negative,
	• long or short term,
	• financial.
	Are there any incentives to encourage you?	

Environmental context and resources	In what way is prescribing for an older patient affected by different clinical situations? • Are there any competing tasks or time constraints that influence whether you might consider level of kidney function when prescribing?	
Social/professional role and identity	Do you sometimes feel constrained by guidelines or recommendations? • Is there anything about your professional role that influences you managing older patients with RKF? (?consensus in your profession)	
Emotion	Would you feel worried about this? • If so, in what ways and in what kind of circumstances? • How would it influence your work stress to...?	
Social influences	Would other team members have a view on you ......? • Who else? Other clinicians, medical staff, relatives? • What do you think those views might be? • How might the views of other team members affect you....?	
Nature of the behaviour	The evidence from research suggests that following recommendations might reduce the risk of harm for patients. With that in mind • What might need to be done differently? • What would you do differently? • Who needs to do what differently when, where, how, how often and with whom? •	
Behavioural regulation	If you are thinking about changing your own practice, how would you do this? • What might you do in order to ... • Are there any procedures or ways of working that might encourage you to ....?	

8.12 Appendix 13: University of Leeds School of Healthcare Ethics approval letter for the GP interview study (Chapter 4)

Faculty of Medicine and Health
Research Office

University of Leeds
Worsley Building
Clarendon Way
Leeds LS2 9NL
United Kingdom

r +44 (0) 113 343 4361

UNIVERSITY OF LEEDS

28 August 2013

Mrs Su Wood
Windhill Green Medical Practice
2 Thackley Old Road
Shipley
West Yorkshire
BD18 1QB

Dear Su

Ref no: SHREC/RP/346

Title: An exploration into prescribing for the older patient with reduced kidney function.

Thank you for making the requested amendments to the documentation for the above project following review by the School of Healthcare Research Ethics Committee (SHREC). I can confirm a favourable ethical opinion based on the documentation received at date of this letter and granted subject to the following condition:

- **No research commences until Trust R&D has confirmed that either approval has been granted or is not required and only Clinical Directorate approval is needed** (Please provide confirmation of approval to the committee when it has been received)

Document	Version	Date Submitted
UNIVERSITY OF LEEDS RESEARCH ETHICS COMMITTEE APPLICATION FORM Su Wood PB in RKF v1 June 2013_tr	1	06.06.13
Topic guide Su Wood PB in RKF v1 June 2013	1	06.06.13
SHREC-Consent-Form Su Wood PB in RKF v1 June 2013	1	06.06.13
SHREC-Information-Sheet Su Wood PB in RKF v1 June 2013	1	06.06.13
Interview invite letter Su Wood PB in RKF Vs1	1	26.07.13
Low Risk Fieldwork RA form Su Wood PB in RKF Vs1 July 2013	1	26.07.13
SHREC-Consent-Form Su Wood PB in RKF Vs2 July 2013	2	26.07.13
SHREC-Information-Sheet Su Wood PB in RKF Vs2 July 2013	2	26.07.13
Interview invite letter Su Wood PB in RKF Vs2 Aug 2013	2	08.08.13
SHREC-Consent-Form Su Wood PB in RKF Vs3 Aug 2013	3	08.08.13
SHREC-Information-Sheet Su Wood PB in RKF Vs3 Aug 2013	3	08.08.13

Please notify the committee if you intend to make any amendments to the original research as submitted at date of this approval. This includes recruitment methodology and all changes must be ethically approved prior to implementation. Please contact the Faculty Research Ethics Administrator for further information FMHUniEthics@leeds.ac.uk

Ethical approval does not infer you have the right of access to any member of staff or student or documents and the premises of the University of Leeds. Nor does it imply any right of access to the premises of any other organisation, including clinical areas. The SHREC takes no responsibility for you gaining access to staff, students and/or premises prior to, during or following your research activities.

Please note: You are expected to keep a record of all your approved documentation, as well as documents such as sample consent forms, and other documents relating to the study. This should be kept in your study file, and may be subject to an audit inspection. If your project is to be audited, you will be given at least 2 weeks notice.

It is our policy to remind everyone that it is your responsibility to comply with Health and Safety, Data Protection and any other legal and/or professional guidelines there may be.

The committee wishes you every success with your project.

Yours sincerely

Kuldip Kaur Bharj

Dr Kuldip Bharj, OBE
Acting Chair, School of Healthcare Research Ethics Committee

8.13 Appendix 14: WSYB CSU NHS research governance assurance letter for the GP interview study (Chapter 4)

Date: 05 November 2013
Reference: 001_05_11_13_0000

NHS

**West and South Yorkshire and Bassetlaw
Commissioning Support Unit**

Research Manager
Paul Carder
Tel: 01274 237406
paul.carder@wsybcsu.nhs.uk

Senior Associate: Research
Rebecca Harper
Tel: 01274 237690
rebecca.harper@wsybcsu.nhs.uk

Mrs Su Wood
39 Emmott Drive
Rawdon
Leeds
LS19 6RE

Re: NHS Research Governance Assurance

Study Title: An Exploration into Prescribing Behaviour for Older People with RKF v1

Ref no: 001_05_11_13_0000

Thank you for your recent submission to NHS West and South Yorkshire and Bassetlaw Commissioning Support Unit.

Following the successful completion of the Research Management & Governance (RM&G) process, we are pleased to provide assurance that all appropriate NHS research governance checks have been completed for the following NHS Primary Care areas:

Bradford City CCG
Bradford District CCG
Leeds North CCG
Leeds South and East CCG
Leeds West CCG

Please note – This letter assures independent contractors in the above areas that the Research Management & Governance (RM&G) process has been completed. Each independent contractor will decide whether to participate following this assurance and will confirm separately.

The following conditions of assurance will apply:
You should be aware that assurance is granted subject to the conditions specified below:
- If required you must obtain an honorary contract and Letter of Access from NHS West and South Yorkshire and Bassetlaw Commissioning Support Unit prior to commencing your study.
- Throughout the course of the study, all research activity should comply with relevant, current governance and regulatory requirements including (but not limited to)

Date: 05 November 2013
Reference: 001_05_11_13_0000

- o The Research Governance Framework for Health and Social Care, 2nd Ed (2005)
- o The Medicines for Human Use (Clinical Trials) Regulations (2004) and subsequent amendments
- o The Mental Capacity Act (2005)
- o The Ionising Radiation (Medical Exposure) (Amendment) Regulations (2006)
- o The Medical Devices Regulations (2002) (Statutory Instrument 2002/618)
- o The Human Tissue Act (2004)
- o The Data Protection Act (1998)

- Consent for NHS West and South Yorkshire and Bassetlaw Commissioning Support Unit to monitor and audit your project, which is implicit in your acceptance of this assurance.
- Where any amendments, substantial or non substantial are made throughout the course of the study these should be notified to NHS West and South Yorkshire and Bassetlaw Commissioning Support Unit on the relevant form (available from http://myresearchproject.org)
- A copy of the final study report should be forwarded to NHS West and South Yorkshire and Bassetlaw Commissioning Support Unit on the relevant form (available from http://myresearchproject.org) no later than 3 months following study completion
- Should any serious adverse event(s) occur throughout the course of the study these should be notified to NHS West and South Yorkshire and Bassetlaw Commissioning Support Unit using the contact details set out above

Should you require any clarification regarding any of the points raised above, or have any further queries in relation to this assurance and post assurance study management process then please do not hesitate to contact Rebecca Harper on 01274 237690.

Finally, may we take this opportunity to wish you well with your study and look forward to hearing about your progress in due course.

Yours sincerely

Erica Warren
Principle Associate for Transformation: Experts and Research Service
NHS West and South Yorkshire and Bassetlaw Commissioning Support Unit
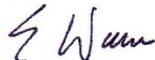
The documents reviewed were:

Document	Version	Date
UREC (SHREC) Favourable Opinion Letter	SHREC/RP/346	
Topic Guide PB in RKF	1	06 June 2013
Low Risk Fieldwork RA Form	1	26 July 2013
Interview Invite Letter	2	08 August 2013
SHREC Consent Form	3	08 August 2013
SHREC Information Sheet	3	08 August 2013
R&D Form	3.5	04 November 2013
SSI Form	3.5	18 September 2013

Date: 05 November 2013
Reference: 001_05_11_13_0000

Evidence of Insurance/Indemnity	NHE-03CA02-0013/RKK665002	19 September 2013

Cc:

- Professor D. K. Theo Raynor
  School of Healthcare
  Baines Wing
  University of Leeds
  LS2 9UT

- Dr. Duncan Petty
  School of Healthcare
  Baines Wing
  University of Leeds
  LS2 9UT

- Professor Robbie Foy
  Charles Thackrah Building
  University of Leeds
  101 Clarendon Road
  Leeds
  LS2 9LJ

- Dr. Liz Glidewell
  Charles Thackrah Building
  University of Leeds
  101 Clarendon Road
  Leeds
  LS2 9LJ

8.14 Appendix 15: WSYBCSU letter of access for the GP interview study (Chapter 4)

Date: 24 April 2014
Reference: 001_05_11_13_0000

NHS

West and South Yorkshire and Bassetlaw Commissioning Support Unit

Research Manager
Paul Carder
Tel: 01274 237406
paul.carder@wsybcsu.nhs.uk

Senior Associate: Research
Rebecca Harper
Tel: 01274 237690
rebecca.harper@wsybcsu.nhs.uk

Mrs Susan Wood
39 Emmott Drive
Rawdon
Leeds
LS19 6RE

Dear Susan,

Letter of access for research
This letter confirms your right of access to conduct research within the following NHS Primary Care areas for the purpose and on the terms and conditions set out below;

Bradford City CCG
Bradford Districts CCG

This right of access commences on 24th April 2014 and ends on 31st March 2016 unless terminated earlier in accordance with the clauses below. You have a right of access to conduct such research as confirmed in writing in the letter of assurance for research from this NHS organisation. Please note that you cannot start the research until the Principal Investigator for the research project has received a letter from us giving assurance to conduct the project.

The information supplied about your role in research at NHS West and South Yorkshire and Bassetlaw Commissioning Support Unit has been reviewed and you do not require an honorary research contract with this NHS organisation. We are satisfied that such pre-engagement checks as we consider necessary have been carried out.

You are considered to be a legal visitor to the NHS premises within the CCG areas detailed above. You are not entitled to any form of payment or access to other benefits provided by this NHS organisation to employees and this letter does not give rise to any other relationship between you and this NHS organisation, in particular that of an employee.

Please note – This letter assures independent contractors in the above areas that the Research Management & Governance (RM&G) process has been completed. Each independent contractor will decide whether to participate following this assurance and will confirm separately.

While undertaking research through NHS West and South Yorkshire and Bassetlaw Commissioning Support Unit, you will remain accountable to your place of study, University of Leeds, but you are required to follow the reasonable instructions of Mr Paul Carder, Research Manager in this NHS

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organisation or those given on his behalf in relation to the terms of this right of access. Where any third party claim is made, whether or not legal proceedings are issued, arising out of or in connection with your right of access, you are required to co-operate fully with any investigation by this NHS organisation in connection with any such claim and to give all such assistance as may reasonably be required regarding the conduct of any legal proceedings.

You must act in accordance with NHS West and South Yorkshire and Bassetlaw Commissioning Support Unit policies and procedures, which are available to you upon request, and the Research Governance Framework 2005. You are required to co-operate with NHS West and South Yorkshire and Bassetlaw Commissioning Support Unit in discharging its duties under the Health and Safety at Work etc Act 1974 and other health and safety legislation and to take reasonable care for the health and safety of yourself and others while on NHS West and South Yorkshire and Bassetlaw Commissioning Support Unit premises. You must observe the same standards of care and propriety in dealing with patients, staff, visitors, equipment and premises as is expected of any other contract holder and you must act appropriately, responsibly and professionally at all times.
You are required to ensure that all information regarding patients or staff remains secure and strictly confidential at all times. You must ensure that you understand and comply with the requirements of the NHS Confidentiality Code of Practice and the Data Protection Act 1998.

http://www.dh.gov.uk/assetRoot/04/06/92/54/04069254.pdf

Furthermore you should be aware that under the Act, unauthorised disclosure of information is an offence and such disclosures may lead to prosecution.

You should ensure that, where you are issued with an identity or security card, a bleep number, email or library account, keys or protective clothing, these are returned upon termination of this arrangement. Please also ensure that while on the premises you wear your ID badge at all times, or are able to prove your identity if challenged. Please note that this NHS organisation accepts no responsibility for damage to or loss of personal property.

We may terminate your right to attend at any time either by giving seven days' written notice to you or immediately without any notice if you are in breach of any of the terms or conditions described in this letter or if you commit any act that we reasonably consider to amount to serious misconduct or to be disruptive and/or prejudicial to the interests and/or business of this NHS organisation or if you are convicted of any criminal offence. Your substantive employer is responsible for your conduct during this research project and may in the circumstances described above instigate disciplinary action against you. NHS West and South Yorkshire and Bassetlaw Commissioning Support Unit will not indemnify you against any liability incurred as a result of any breach of confidentiality or breach of the Data Protection Act 1998. Any breach of the Data Protection Act 1998 may result in legal action against you and/or your substantive employer.

If your current role or involvement in research changes, or any of the information provided in your Research Passport changes, you must inform your employer through their normal procedures. You must also inform your nominated manager in this NHS organisation.

Yours sincerely

Rebecca Harper – Senior Associate: Research
NHS West and South Yorkshire and Bassetlaw Commissioning Support Unit

www.wsybcsu.nhs.uk

8.15 Appendix 16: participant invitation letter for the consensus group study (Chapter 5).

Leeds School of Healthcare
Leeds Institute of Health Sciences
Faculty of Medicine and Health

Baines Wing
University of Leeds
Leeds LS2 9JT

UNIVERSITY OF LEEDS

Su Wood

Phone: 07866837665
e-mail: hcs9s4w@leeds.ac.uk

Version 1, 12/01/2015

12th January 2015

Insert name
Insert address

Dear Insert name of patient/professional

Development of an intervention strategy to produce behaviour change in prescribing for older people with reduced kidney function through a consensus group

I am writing ask for your help with this research project. I am a pharmacist currently working in Bradford Districts Clinical Commissioning Group practices as well as doing a PhD at the University of Leeds School of Healthcare in partnership with the Academic Unit of Primary Care. A practice audit and PCT-wide survey have suggested that recommendations for use and dosing of drugs for older patients with reduced kidney function are not often applied, and a GP interview study has sought the experience, perspective and views on prescribing for older patients with reduced kidney function. We are hoping that the ultimate outcome of this project will be to help practitioners with this area of prescribing.

This project aims to develop an intervention strategy to produce behaviour change to improve prescribing for older people with reduced kidney function with a group of stakeholders and experts related to the field, and to gain consensus on a plan for future research on behaviour change implementation. Findings from this study will be used to inform development of an intervention that is likely to be useable, feasible and effective to help make it easier to apply recommendations on drug and dosing in reduced kidney function for older people. Further information on the project can be found in the accompanying 'Participant Information Sheet'.

The group consensus process involves initially rating a series of statements and taking part in a group discussion. The statement rating may take up to 1 hour and the group exercise will aim to last 1-1.5 hours. A certificate of attendance at interview will be given for CPD/ recognition of participation in research, where appropriate. Food will be provided at the group discussion.

This study has been reviewed and approved by the University of Leeds School of Healthcare Research Ethics Committee (Approval number SHREC/RP/512). If you would like any additional information please contact Su Wood (mob:07866837665).

Once you have completed the attached consent form, all you have to do is return it in the **FREEPOST** envelope provided. Please return the slip if you do not wish to be approached for this study so that I do not contact you again.

Many thanks for your time.

Yours sincerely

Su Wood   **On behalf of the research team**
PhD student

Su Wood Consensus Panel: participant invite letter Vs1 Jan 2015

8.16 Appendix 17: participant consent form for the consensus group study (Chapter 5)

Leeds School of Healthcare
Leeds Institute of Health Sciences
Faculty of Medicine and Health

Baines Wing
University of Leeds
Leeds LS2 9JT

UNIVERSITY OF LEEDS

Participant Consent Form
Vs1 12/01/15

Name of Centre: School of Healthcare and Academic Unit of Primary Care, University of Leeds

Title of Study: Development of an intervention strategy to produce behaviour change in prescribing for older people with reduced kidney function through a consensus group

	Please confirm agreement to the statements by putting your initials in the box below
I have read and understood the participant information sheet	
I have had the opportunity to ask questions and discuss this study	
I have received satisfactory answers to all of my questions	
I have received enough information about the study	
I understand that I am free to withdraw from the study at any time without having to give a reason; however, I will not be able to withdraw any data two weeks after the group exercise because it will have been anonymised and analysed.	
I understand that the group exercise will be audio-recorded.	
I understand that any information I provide, including personal details, will be kept confidential, stored securely and only accessed by those carrying out the study.	
I understand that any information I give may be included in published documents but all information will be anonymised.	
I understand that findings from this study will be used to inform development of an intervention that is likely to be useable, feasible and effective to help make it easier to apply recommendations on drug and dosing in reduced kidney function.	
I agree to take part in this study	

Participant Signature ....   Date

Name of Participant

Researcher Signature ....   Date

Name of Researcher

Thank you for agreeing to take part in this study.

8.17 Appendix 18: participant information sheet for the consensus group study (Chapter 5)

Leeds School of Healthcare
Leeds Institute of Health Sciences
Faculty of Medicine and Health

Baines Wing
University of Leeds
Leeds LS2 9JT

UNIVERSITY OF LEEDS

Consensus Panel Participant Information Sheet

Development of an intervention strategy to produce behaviour change in prescribing for older people with reduced kidney function through a consensus group

Version 1 Date: 12/01/2015

You are being invited to take part in a research study. Before you decide, it is important for you to understand why the research is being done and what it will involve if you decide to take part. Please take the time to read the following information carefully and discuss it with others if you wish. Ask Su Wood (details below) if there is anything that is not clear or if you would like more information. Thank you for taking the time to read this.

What is the research about?
This study aims to develop an intervention strategy to produce behaviour change to improve prescribing for older people with reduced kidney function, and to gain consensus on a plan for future research. Findings from this study will be used to inform development of an intervention that is likely to be useable, feasible and effective to help make it easier to apply recommendations on drug and dosing in reduced kidney function.

Who is doing this study?
Su Wood, the principal investigator, is doing this study as part of a PhD research project with help from a team of researchers at Leeds University. Su Wood will be a facilitator for the group discussion along with a co-facilitator from the research team.

Why have I been asked to participate?
You have been identified as a stakeholder and expert related to the field of prescribing for the older patient with reduced kidney function and reducing risk from prescribing.

Do I have to take part?
No. If you do not want to take part you do not have to. You do not have to give a reason.

What will be involved if I take part in this study?
If you decide to take part, we would like to invite you to initially individually rate a series of statements. You will then be invited to a group exercise to discuss the research findings and ideas for future research, at the end of which, the group will come to a consensus agreement on the statements and priorities for intervention strategy and future research.

The statement rating should take no longer than 1 hour; the group exercise is expected to last approximately 1-1.5 hours. With your prior agreement the group exercise will be audio-recorded.

What are the advantages and disadvantages of taking part?
By taking part in this research you will help to inform development of an intervention that is likely to be useable, feasible and, and to prioritise areas for future research.

A certificate of attendance at interview will be given for CPD and/or recognition of your participation in this research project.

We do not think that taking part in the discussion will cause any disadvantages to you apart from taking your time. We appreciate that you will have a very busy schedule and hope to minimise disruption by holding the group exercise at a time to suit you.

Can I withdraw from the study at any time?
You will be able to withdraw from the study at any time without giving a reason. However, you will not be able to withdraw any data two weeks after the group exercise because it will have been anonymised and analysed.

Will the information I give be kept confidential?
Yes, all information that identifies you will be strictly confidential and held securely at the University of Leeds; data handling procedures will be in accordance with the Data Protection Act 1998.

The audio recordings of the group exercise will be used to confirm statements, where required. The audio recordings will be destroyed once analysis and research has been completed. The anonymous information will be stored securely. All other personal information e.g. names or numbers that could identify you will be kept separately in a secure location at the University of Leeds.

What will happen to the results of the study?
The results of the study will be presented and published. You will receive a summary of our findings. It will not be possible to identify you from any reports about the project.

Who has reviewed this study?
All research in the NHS is looked at by Research Ethics Committees to protect your interests. Ethical approval has been granted by the School of Healthcare Research Ethics Committee:-
Project reference number: SHREC/RP/512
Date: 16/3/15

If you agree to take part, would like more information or have any questions or concerns about the study please contact Su Wood by phone on 07866837665 or email (hcs9s4w@leeds.ac.uk)

Lead supervisor: Prof D. K. Raynor email: D.K.Raynor@leeds.ac.uk telephone: 0113 343 1442
Thank you for taking the time to read this information sheet.

8.18 Appendix 19: certificate of attendance for the consensus group study (Chapter 5)

Leeds School of Healthcare
Leeds Institute of Health Sciences
Faculty of Medicine and Health

Baines Wing
University of Leeds
Leeds LS2 9JT

UNIVERSITY OF LEEDS

Certificate of attendance

Research study: Development of an intervention strategy to produce behaviour change in prescribing for older people with reduced kidney function through a consensus group

………………………………………………… participated in a consensus group process by:

- individually rating a series of statements on what needs to change in prescribing for older people with reduced kidney function.

- taking part in a group discussion on the research findings and the key themes.

- Agreeing priorities for an intervention strategy that is likely to be useable, feasible and effective to help make it easier to apply recommendations on drug and dosing in reduced kidney function.

Individual statement rating = 1 hour
Group discussion   = 2 hours

Signed……………………………………………… Date……………………………

Su Wood PhD study June 2015

8.19 Appendix 20: University of Leeds School of Healthcare ethics approval letter for the consensus panel study (Chapter 5)

Faculty of Medicine and Health

Research Office

University of Leeds
Worsley Building
Clarendon Way
Leeds LS2 9NL
United Kingdom

℅ +44 (0) 113 343 2274

UNIVERSITY OF LEEDS

16 March 2015

Mrs Su Wood
Windhill Green Medical Practice
2 Thackley Old Road
Shipley, W Yorks
BD18 1QB

Dear Su

Ref no: SHREC/RP/512

Title: Development of an intervention strategy to produce behaviour change in prescribing for older people with reduced kidney function through a consensus group

Thank you for submitting your documentation for the above project. Following review by the School of Healthcare Research Ethics Committee (SHREC), I can confirm a favourable ethical opinion based on the documentation received at date of this letter and granted subject to the following condition(s):

- Trust R&D approval must be obtained prior to commencement of the research and confirmation of this approval sent to this committee once obtained

Document	Version	Date Submitted
Ethical_Review_Form_V3 Su Wood Consensus panel Feb 2015	1	06.02.15
Interview invite letter Su Wood Consensus Panel Vs1 Jan 2015.doc1	1	06.02.15
Low Risk Fieldwork RA form Su Wood Consensus Panel Vs1 Jan 2015_tr	1	06.02.15
SHREC-Consent-Form Su Wood Consensus Panel Vs1 Jan 2015	1	06.02.15
SHREC-Information-Sheet Su Wood Consensus Panel Vs1 Jan 2015	1	06.02.15
SHRECRP512 Reviewer Comments response	1	04.03.15

Please notify the committee if you intend to make any amendments to the original research as submitted at date of this approval. This includes recruitment methodology and all changes must be ethically approved prior to implementation. Please contact the Faculty Research Ethics Administrator for further information FMHUniEthics@leeds.ac.uk

Ethical approval does not infer you have the right of access to any member of staff or student or documents and the premises of the University of Leeds. Nor does it imply any right of access to the premises of any other organisation, including clinical areas. The SHREC takes no responsibility for you gaining access to staff, students and/or premises prior to, during or following your research activities.

Please note: You are expected to keep a record of all your approved documentation, as well as documents such as sample consent forms, and other documents relating to the study. This should be kept in your study file, and may be subject to an audit inspection. If your project is to be audited, you will be given at least 2 weeks notice.

It is our policy to remind everyone that it is your responsibility to comply with Health and Safety, Data Protection and any other legal and/or professional guidelines there may be.

The committee wishes you every success with your project.

Yours sincerely

Kuldip Kaur Bharj

Dr Kuldip Bharj, OBE
Chair, School of Healthcare Research Ethics Committee

8.20 Appendix 21: NHS research governance assurance letters for the consensus panel study (Chapter 5)

Date: 27th May 2015
Reference: 001_27_05_15_0000

NHS

**Leeds West
Clinical Commissioning Group**

Mrs Susan Wood
PhD Student
The School of Healthcare, Baines Wing
University of Leeds
Leeds, LS2 9JT

Re: Consensus Intervention Strategy Development for Rx in RKF

Ref no: 001_27_05_15_0000

Thank you for your recent submission to NHS Leeds West Clinical Commissioning Group (CCG) Following consideration of your submission I am pleased to confirm that research management and governance permission has been granted by NHS Leeds West CCG for the above research to take place as described in your completed application and accompanying documentation.

Conditions of permission
You should be aware that permission is granted subject to the conditions specified below:
- If required you must obtain an honorary contract and Letter of Access from NHS Leeds West CCG prior to commencing your study.
- All Global Governance checks must be completed on CSP Module
- All Local Governance must be completed on CSP Module
- Throughout the course of the study, all research activity should comply with relevant, current governance and regulatory requirements including (but not limited to)

  o The Research Governance Framework for Health and Social Care, 2nd Ed (2005)
  o The Medicines for Human Use (Clinical Trials) Regulations (2004) and subsequent amendments
  o The Mental Capacity Act (2005)
  o The Ionising Radiation (Medical Exposure) (Amendment) Regulations (2006)
  o The Medical Devices Regulations (2002) (Statutory Instrument 2002/618)
  o The Human Tissue Act (2004)
  o The Data Protection Act (1998)

- Consent for NHS Leeds West CCG to monitor and audit your project, which is implicit in your acceptance of permission.
- Where any amendments, substantial or non substantial are made throughout the course of the study these should be notified to NHS Leeds West CCG on the relevant form (available from http://myresearchproject.org)
- A copy of the final study report should be forwarded to NHS Leeds West CCG on the relevant form (available from http://myresearchproject.org) no later than 3 months following study completion.
- Should any serious adverse event(s) occur throughout the course of the study these should be notified to NHS Leeds West CCG using the contact details set out above

Should you require any clarification regarding any of the points raised above, or have any further queries in relation to permissions and post permission study management process then please do not hesitate to contact Paul Carder on 01274 237406.

Finally, may I take this opportunity to wish you well with your study and look forward to hearing about your progress in due course.

Yours sincerely
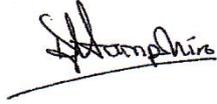
Diane Hampshire
Director of Quality and nursing
NHS Leeds West CCG

The documents reviewed were:

Document	Version	Date
SCHREC Approval Letter	SCHREC/RP/512	16 March 2015
Protocol	1	January 2015
Participant Information Sheet Consensus Panel	1	12 January 2015
Consent Form Consensus Panel	1	12 January 2015
Consensus Panel: Statement Rating Survey	1	22 May 2015
RAND Appropriateness Method		
BOS Licence		
Participant Invitation Letter	1	1 January 2015
Fieldwork Assessment Form	1	05 February 2015
Chief Investigator/Student/PI CV – Susan Wood		21 March 2015
Academic Supervisor 1 CV – Prof D.K. Theo Raynor		
Academic Supervisor 2 CV – Dr Liz Glidewell		
Academic Supervisor 3 CV – Dr Duncan Petty		
Evidence of insurance/indemnity	NHE-03CA02-0013/RKK665002	17 September 2014
NHS R&D Form	4.0.0	22 May 2015
NHS SSI Form – Leeds West CCG	4.0.0	21 May 2015

Cc. (via email)
-Professor D.K.Theo Raynor
 School of Healthcare, University of Leeds

-Dr Duncan Petty
 Pharmacy Department, University of Bradford

-Dr Liz Glidewell, Charles Thackrah Building, University of Leeds

Mrs Susan Wood
PhD Student
The School of Healthcare, Baines Wing
University of Leeds
Leeds, LS2 9JT

Re: NHS Research Governance Assurance

Study Title: Consensus Intervention Strategy Development for Rx in RKF

Ref no: 001_27_05_15_0000

Thank you for your recent submission to NHS Yorkshire and Humber Commissioning Support.

Following the successful completion of the Research Management & Governance (RM&G) process, we are pleased to provide assurance that all appropriate NHS research governance checks have been completed for the following NHS Primary Care areas:

Bradford Districts CCG

Please note – This letter assures independent contractors in the above areas that the Research Management & Governance (RM&G) process has been completed. Each independent contractor will decide whether to participate following this assurance and will confirm separately.

The following conditions of assurance will apply:
You should be aware that assurance is granted subject to the conditions specified below:
- If required you must obtain an honorary contract and Letter of Access from NHS Yorkshire and Humber Commissioning Support prior to commencing your study.
- Throughout the course of the study, all research activity should comply with relevant, current governance and regulatory requirements including (but not limited to)

  o The Research Governance Framework for Health and Social Care, 2nd Ed (2005)
  o The Medicines for Human Use (Clinical Trials) Regulations (2004) and subsequent amendments
  o The Mental Capacity Act (2005)
  o The Ionising Radiation (Medical Exposure) (Amendment) Regulations (2006)
  o The Medical Devices Regulations (2002) (Statutory Instrument 2002/618)
  o The Human Tissue Act (2004)
  o The Data Protection Act (1998)
- Consent for NHS Yorkshire and Humber Commissioning Support to monitor and audit your project, which is implicit in your acceptance of this assurance.

- Where any amendments, substantial or non substantial are made throughout the course of the study these should be notified to NHS Yorkshire and Humber Commissioning Support on the relevant form (available from http://myresearchproject.org)
- A copy of the final study report should be forwarded to NHS Yorkshire and Humber Commissioning Support on the relevant form (available from http://myresearchproject.org) no later than 3 months following study completion
- Should any serious adverse event(s) occur throughout the course of the study these should be notified to NHS Yorkshire and Humber Commissioning Support using the contact details set out above

Should you require any clarification regarding any of the points raised above, or have any further queries in relation to this assurance and post assurance study management process then please do not hesitate to contact Rebecca Harper on 01274 237690.

Finally, may we take this opportunity to wish you well with your study and look forward to hearing about your progress in due course.

Yours sincerely

Paul Carder
Senior Associate: Research and HEEES
NHS Yorkshire and Humber Commissioning Support

The documents reviewed were:

Document	Version	Date
SCHREC Approval Letter	SCHREC/RP/512	16 March 2015
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Cc. (via email)
-Professor D.K.Theo Raynor   -Dr Duncan Petty
 School of Healthcare, University of Leeds   Pharmacy Department, University of Bradford

-Dr Liz Glidewell, Charles Thackrah Building, University of Leeds

The Leeds Teaching Hospitals **NHS**

NHS Trust

Lucy Williams

22/05/2015

Mrs Susan Wood

Prescribing Support Services
Windhill Green Medical Centre
2 Thackley Old Road
Shipley
BD18 1QB

Research & Innovation

Leeds Teaching Hospitals NHS Trust
34 Hyde Terrace
Leeds
LS2 9LN

Tel: 0113 392 0162
Fax: 0113 392 0146

r&d@leedsth.nhs.uk
www.leedsth.nhs.uk

Dear Mrs Susan Wood

Re: NHS Permission at LTHT for: Development of an intervention strategy to produce behaviour change in prescribing for older people with reduced kidney function through a consensus group
LTHT R&I Number: RL15/124
REC: SHREC/RP/512

I confirm that *NHS Permission for research* has been granted for this project at The Leeds Teaching Hospitals NHS Trust (LTHT). NHS Permission is granted based on the information provided in the documents listed below. All amendments (including changes to the research team) must be submitted in accordance with guidance in IRAS. Any change to the status of the project must be notified to the R&I Department.

The study must be conducted in accordance with the *Research Governance Framework for Health and Social Care*, ICH GCP (if applicable), the terms of the Research Ethics Committee favourable opinion (if applicable) and NHS Trust policies and procedures (see http://www.leedsth.nhs.uk/research/) including the requirements for research governance and clinical trials performance management listed in appendix 1 and 2 . NHS permission may be withdrawn if the above criteria are not met including the requirements for clinical trials performance

The Leeds Teaching Hospitals NHS Trust participates in the NHS risk pooling scheme administered by the NHS Litigation Authority ""Clinical Negligence Scheme for NHS Trusts"" for: (i) medical professional and/or medical malpractice liability; and (ii) general liability. NHS Indemnity for negligent harm is extended to researchers with an employment contract (substantive or honorary) with the Trust. The Trust only accepts liability for research activity with NHS Permission

The Trust therefore accepts liability for the above research project and extends indemnity for negligent harm. Should there be any changes to the research team please ensure that you inform the R&I Department and that s/he obtains an appropriate contract, or letter of access, with the Trust if required.

Yours sincerely

Anne Gowing
Research Governance Manager

Chair Dr Linda Pollard CBE JP DL Chief Executive Julian Hartley

The Leeds Teaching Hospitals incorporating:
Chapel Allerton Hospital   Leeds Dental Institute   Seacroft Hospital   Leeds Children's Hospital
St James's University Hospital   Leeds General Infirmary   Wharfedale Hospital   Leeds Cancer Centre

use the
NHS Number

WFA280
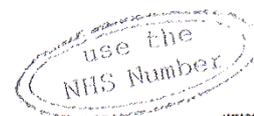
Email from Mark Baker, Director of the NICE Centre for Clinical Practice confirming governance approval for panel member.

Please see below for confirmation from my employer that I am able to participate.

Mark Baker is Director of the NICE Centre for Clinical Practice

Best wishes

From: Mark Baker

Sent: 19 May 2015 17:03

To:

Subject: RE: Consensus panel for PhD student

Yes of course. Sounds really interesting and worthwhile.

M

Sent from my Windows Phone

Sent: 19/05/2015 16:34

To: Mark Baker

Subject: FW: Consensus panel for PhD student

Hi Mark,

I have been asked to take part in a consensus panel for a PhD student at Leeds University (please see email below). It's 12.30-2.30pm on 4/6/15

Johanna and Paul have approved me to do this, but I've just been made aware that the Research Governance Policy also requires approval from a SMT-level Director

Would you be able to approve this please?

Many thanks

8.21 Appendix 22: presentation slides for the consensus group discussion meeting.

Consensus Group

Development of an intervention strategy to produce behaviour change in prescribing for older people with reduced kidney function through a consensus group

Su Wood PhD student

Agenda

- Introductions
- Brief overview of the research project findings
- Discussion around the key themes on
    - what needs to change?
    - what might feasibly be part of an intervention strategy?
- Final choice of top 3 priorities for an intervention strategy.

PhD project

- **Are recommendations for prescribing applied to older patients with reduced kidney function? A mixed methods study to explore and improve implementation.**

- **Focus is on use and dosing of drugs for older people**

- A retrospective study in Sweden by Helldén et al (2009) found that 14% of hospital admissions of elderly patients were primarily caused by ADRs and one-third were related to impaired renal function, generally in very old women.

- The French primary care study by Breton et al (2011) found that the prevalence of inappropriate drug use in reduced renal function was independently related to higher all-cause mortality

- Helldén, A et al. Adverse Drug Reactions and Impaired Renal Function in Elderly Patients Admitted to the Emergency Department: A Retrospective Study. Drugs & Aging:2009; 26; 7; 595-606(12).
- Breton G, Froissart M, Janus N et al. Inappropriate drug use and mortality in community-dwelling elderly with impaired kidney function – the Three-City population-based study. Nephrol Dial Transplant 2011;26:2852-9


Audit by case note review in 5 GP practices

- 594 people aged 65yrs and older with eGFR<60ml/min/1.73m^2 reviewed.
- 25% were on one or more drugs which recommendations suggest should be discontinued or the dose reduced because of the low level of kidney function.
- 70 different drugs implicated.

PCT-wide prescribing database survey

- 70,900 people aged 65yrs and older

- 84.6% of those on the investigation drugs had a kidney function test on the record in the previous 15mths

- 8 drugs/ drug classes investigated

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% people aged ≥65yrs on the drugs
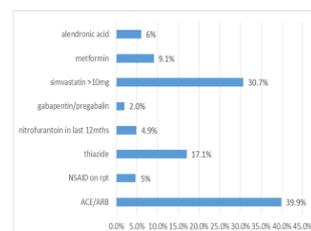
% found with a kidney function too low for the drug prescribed – 85yrs and older

	eGFR	CrCl C&G
Alendronic acid	6.9%	55.2%
Metformin	1.1%	24.2%
Simvastatin	4.4%	32.0%
Gabapentin/ pregabalin	6.7%	20.5%

eGFR vs CrClCG for drug dosing

- Helou's literature review (2010) - when they looked at articles looking specifically at the older patient, they concluded that CG remains the most accurate formula.

- Spruill (2008) concluded that, although MDRD may be useful for estimating GFR, CG should still be used for drug adjustments; the decline in kidney function with age is expressed linearly with CG and exponentially with MDRD

eGFR and CrCl equation effect with age

Female 60kg SrCr 80micromol/L
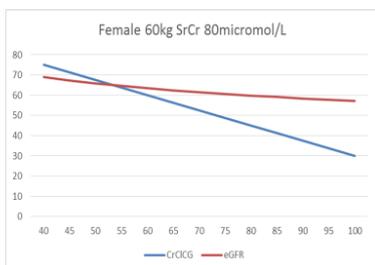
Difference between eGFR and CrCl

age srcr	40	45	50	55	60	65	70	75	80	85	90	95	100
50	-1	2	5	9	13	17	22	26	31	36	41	45	50
60	-4	-1	2	5	8	12	16	20	23	27	31	36	40
70	-5	-3	0	2	5	9	12	15	18	22	25	29	32
80	-6	-4	-2	1	3	6	9	12	15	18	21	24	27
90	-7	-5	-3	0	2	5	7	10	12	15	18	20	23
100	-7	-5	-3	-1	1	3	6	8	10	13	15	18	20
110	-7	-5	-3	-2	0	2	4	7	9	11	13	15	18
120	-7	-5	-4	-2	0	2	4	5	7	10	12	14	16
130	-7	-5	-4	-2	-1	1	3	5	6	8	10	12	14
140	-7	-5	-4	-3	-1	1	2	4	6	7	9	11	13
150	-7	-5	-4	-3	-1	0	2	3	5	7	8	10	12
160	-7	-5	-4	-3	-1	0	1	3	4	6	8	9	11
170	-6	-5	-4	-3	-2	0	1	2	4	5	7	8	10
180	-6	-5	-4	-3	-2	-1	1	2	3	5	6	8	9
190	-6	-5	-4	-3	-2	-1	1	2	3	4	6	7	8
200	-6	-5	-4	-3	-2	-1	0	2	3	4	5	7	8

Roberts et al (2009) used gentamicin drug levels to look at equation effect in older people

- They found that

- MDRD (eGFR) overestimated renal function as age increased (29% and up to 69%) and

- C&G underestimated renal function, though this was of a smaller magnitude (10%), consistent across age, and thus better suited for dose calculation, especially in the elderly;

- age significantly influenced MDRD overestimation in their population (P = 0.037).

NOACs

- Dabigatran – MHRA 'Do not start dabigatran in any patient with severe renal impairment (creatinine clearance <30 mL/min)'

- European Heart Rhythm Association guidelines on NOAC treatment (2013), 'CrCl is best assessed by the Cockcroft method'

Heidbuchel H, Verhamme P, Alings M, et Al. EHRA practical guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation: executive summary. Advance Access published, European Heart Journal.213; DOI: 10.1093/eurheartj/eht134

Key findings

- Most patients do have a kidney function test on the record.

- Many older patients are on these drugs.

- Many older people with reduced kidney function do not have their drugs and doses altered in line with recommendations.

GP interviews

- 15 GPs interviewed across Bradford

- to understand their experience of prescribing for older patients with reduced kidney function.

- Analysis of their responses used to suggest what needs to change

Key theme 1: in primary care there is a lack of awareness, knowledge, and understanding about prescribing in the reduced kidney function of older people.

- *"I suspect for some clinicians, and I include myself in that, there may be a knowledge gap" (P1)*

- *"it's probably one of those areas where there is a bit of a blind side" (P4)*

- *"I wasn't aware. This is terrible because I use a lot of gabapentin and pregabalin, obviously, in neurology" (P6)*

Key theme 2: kidney function testing is required when prescribing for older people.

- *we often check the bloods …..but I don't often drill, ever is probably the right word, drill down to the eGFR to see whether any of the medications that they're on tally with the GFR (P9)*

- *we are very good at knowing when to re-check the U & Es, but are we actually correlating that with what people are on? (P7)*

Key theme 3: the application of kidney function level to prescribing decisions is needed at both drug initiation and at medication review.

- *With the medication review you've just got a list of the drugs in front of you – So you've got to have that knowledge.. well it's got to be in your head (P11)*

- *once they are on the repeats it doesn't then, doesn't then flag it up again [warnings]. (P4)*

- *"when you are continuing something that somebody else has started, this is wrong probably, but you feel less a responsible decision to continue something. That's wrong I admit" (P7)*

- *renal function isn't one of the things that we benchmark against when we review medications, (P12)*

Key theme 4: there is difficulty in remembering to apply the recommendations for use, and dosing, of drugs in reduced kidney function.

- *it's remembering which medications you need to be careful with, those are the pitfalls. (P12)*

- *I think it's so QOF orientated now, you know we are focused on perhaps the wrong stuff in medication reviews. (P7)*

- *the reality is that the world we live in in general practice is there are lots of boxes to tick – have you checked the blood pressure, have you done the BMI, code this, code that, do that, (P1)*

Key theme 5: there is a need for to embed kidney function assessment within the prescribing process.

- *It [prescribing] is so complex, as is medicine, increasingly complex, so that to rely on human functions to pick up everything, there are bound to be mistakes (P1)*

- *"I need a button to just.. check on to highlight all drugs that are a problem" (P15)*

Key theme 6: there is limited use and confusion with the resources available to support the use, and dosing, of drugs in reduced kidney function.

- *I was just looking at what the BNF said about the rivaroxaban...cos I wanted to know whether it talks about creatinine clearance, no it doesn't , it talks about eGFR -following the BNF would give her too much rivaroxaban (P4)*

- *I should read that (looking at the BNF section on prescribing in renal impairment) (P2)*

- *The ageing population is going to make it bigger! We're just prescribing more and more stuff aren't we? (P13)*