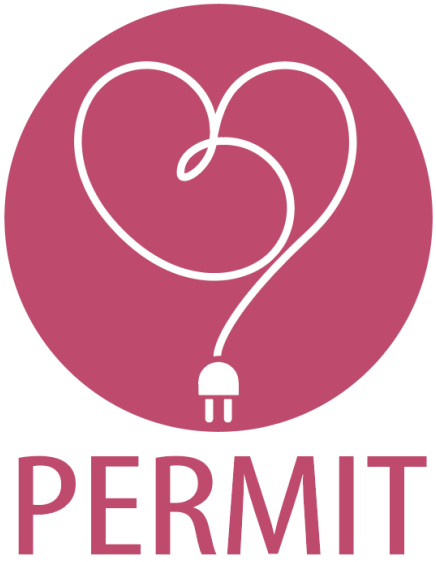
THE PERMIT PROJECT:

PERSONALISED RENAL FUNCTION MONITORING VIA INFORMATION TECHNOLOGY



Thesis submitted in accordance with the requirements of the University of Liverpool for the degree of Doctor in Philosophy by

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DECLARATION

This dissertation is the result of my own work. It has not been previously submitted, in part or whole, to any university of institution for any degree, diploma, or other qualification.

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Abstract

Patients with heart failure are typically elderly and are among those most at risk of renal failure due to both their condition and their medication. Regular monitoring of renal function may allow early detection of renal decline and appropriate intervention to prevent renal failure. However, clinical guidance on renal function monitoring in heart failure is sparse and based on anecdotal evidence. To reduce unnecessary admissions caused by renal impairment in heart failure due to inadequate monitoring, standardised practice for renal monitoring would be of benefit. Given that each patient has individual co-morbidities and rates of renal decline, general guidelines may have minimal impact and there may be a need for renal monitoring that is personalised case-by-case. The aim of the PERMIT project (Personalised renal function monitoring via information technology) was to develop the framework for creating such personalised guidance by using machine-learning on large clinical datasets. The goal was to create a prediction model that could highlight which patients with heart failure were most at risk of renal decline, in order to intervene before they required hospital admission.

In light of developing a future predictive algorithm for use in clinical care, patient and clinician engagement with heart failure-related remote healthcare technologies was investigated. The aim of this was to improve the knowledge base so that future technologies, such as remote renal monitoring, can improve upon their accessibility and acceptability in this patient cohort. Studies examining remote care in heart failure were thematically synthesised in a qualitative systematic review. This generated 5 core themes of engagement: Clinical Care, Convenience, Communication, Ease of use, and Education, with different perspectives from patients and healthcare staff. The themes which were generated were assessed prospectively via a discrete-choice questionnaire survey given to heart failure patients (n=93). Binary logit analysis showed that ‘Clinical care’ was most valued by patients with heart failure and was almost twice as important as ‘Communication’, the lowest ranked theme. The study provided important insights into the lived experiences of patients with heart failure that will allow the development of future interventions with greater acceptability and engagement rates.

To create the predictive model for renal decline, retrospective primary care data was obtained from SIR (Salford Integrated Records). This data was processed into a longitudinal dataset which included 3800 adult patients with newly diagnosed heart failure, over an 8.5 year study window. The clinical parameters of each patient were mapped longitudinally with creatinine over time. A model-based clustering algorithm known as ‘flexmix’ was applied to the data. In order to select appropriate clinical variables to input into the clustering predictive model, pairwise mixed-model linear regression was used to determine correlation between each clinical parameter and log(creatinine). The most correlative covariates were serum urea and serum potassium, with urea showing the highest R-squared value for explaining variance in creatinine over time. The final clustering model therefore used the inputs of: age at heart failure diagnosis; time since heart failure diagnosis; gender; IMD decile; and serum urea. This process produced seven discrete clusters of renal change over time which were ranked by severity. Evaluation of the algorithm was made using the assigned cluster models to predict creatinine over time in patients with heart failure. The MAPE (mean absolute percentage error) of the creatinine prediction was between 17-33% depending on the cluster assigned.

The work outlined in this thesis represents an important step towards developing personalised renal monitoring guidance. Important clinical correlates of renal function decline, identified in the process, can be used for prognostic research in future studies. The error of the prediction values was variable and will thus require further optimisation using additional datasets and clinical studies in the future.

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Academic outputs

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Prizes

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List of Abbreviations and Acronyms

ACCF	American College of Cardiology Foundation
ACEi	Angiotensin converting enzyme inhibitor
ACR	Albumin:creatinine ratio
ADE	Adverse drug event
ADR	Adverse drug reaction
AF	Atrial fibrillation
AHA	American Heart Association
AKI	Acute kidney injury
ANN	Artificial neural network
ANP	Atrial natriuretic peptide
ARB	Angiotensin receptor blocker
AUC	Area under the curve
BIC	Bayesian Information Criterion
BH	Benjamini-Hochberg
BMI	Body mass index
BNP	Brain natriuretic peptide
BUN	Blood urea nitrogen
BW	Body weight
CASP	Critical Appraisal Skills Programme
CCF	Congestive heart failure
CCG	Clinical commissioning group
CENTRAL	Cochrane Central Database of Controlled Trials
CHF	Chronic heart failure
CKD	Chronic kidney disease
CKD-EPI	Chronic kidney disease epidemiology collaboration equation for eGFR
CLAHRC	Collaboration for Leadership in Applied Health Research and Care
CO	Cardiac output
COPD	Chronic obstructive pulmonary disease
COREQ	Consolidated Criteria for Reporting Qualitative Research
CPRD	Clinical practice research database
CRP	C-reactive protein
CRS	Cardio-renal syndrome
CRT	Cardiac resynchronisation therapy
CSDR	Cochrane Database of Systematic Reviews
CVD	Cardiovascular disease

CVP	Central venous pressure
DARE	Database of abstracts of Reviews of Effects
DF	Date flag
DBP	Diastolic blood pressure
DCE	Discrete choice experiment
DMT2	Diabetes mellitus type 2
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
EHR	Electronic health records
EM	Expectation-Maximisation algorithm
EPO	Erythropoietin
ENTREQ	Enhancing Transparency in Reporting the Synthesis of Qualitative Research
ESC	European Society of Cardiology
FCN	Final number of clusters
FHx	Family history
GFR	Glomerular filtration rate
Hb	Haemoglobin
HbA1c	Haemoglobin A1c / glycated haemoglobin
HDL	High-density lipoprotein
HF	Heart failure
HR	Heart rate
HTN	Hypertension
ICD	Implantable cardio-defibrillator
ICL	Integrated completed likelihood
ICU	Intensive Care Unit
IHD	Ischaemic heart disease
IMD	Indices of multiple deprivation
ISDN	Isosorbide dinitrate
K	Starting number of clusters
KDIGO	Kidney Disease Improving Global Outcomes guidelines
LCCG	Liverpool clinical commissioning group
LSOA	Lower super output area
LV	Left ventricle
LVEDV	Left ventricular end-diastolic volume
LVEF	Left ventricular ejection fraction
MCV	Mean corpuscular volume
MDRD	Modification of Diet in Renal Disease study equation for eGFR
MAPE	Mean absolute percentage error

MRA	Mineralocorticoid receptor antagonist
NICE	National Institute for Health and Care Excellence
NKCC	Sodium-potassium-chlorine cotransporter
NO	Nitric oxide
NOAC	Novel oral anticoagulant
NSAID	Non-steroidal anti-inflammatory
NT pro-BNP	End terminal pro-BNP
NWC	North West Coast
PE	Pulmonary embolism
PERMIT	Personalised Renal Monitoring via Information Technology
PP	Pulse pressure
PPI	Patient Public Involvement
PVD	Peripheral vascular disease
RA	Rheumatoid arthritis
RAA	renin-angiotensin-aldosterone
RMSE	Root mean square error
RRT	Renal replacement therapy
RRD	Rate of renal decline
RV	Right ventricle
SAIL	The Secure Anonymised Information Linkage Databank
SBP	Systolic blood pressure
SE	Standard error
SIGN	Scottish Intercollegiate Guidelines Network
SLE	Systemic lupus erythematosus
SV	Stroke volume
TIN	Tubulointerstitial nephritis
UTI	Urinary tract infection
WRF	Worsening renal function criteria

CHAPTER 1

GENERAL INTRODUCTION

CHAPTER 1: GENERAL INTRODUCTION

1.1 Heart failure and renal decline

Heart failure is associated with high levels of morbidity and mortality in the UK, and is likely to increase in prevalence as the population ages. The overall incidence of heart failure is 1%, rising to around 12% in patients over 75 years. It currently affects up to 900,000 patients in the UK.[1] These patients often suffer from co-morbidities including diabetes, chronic obstructive pulmonary disease (COPD) and ischaemic heart disease resulting in frequent hospital admissions and greater burden on the health service.[2] One of the most common causes of hospital admission and deterioration in these patients is worsening renal function, which includes acute kidney injury (AKI).[3] A single severe episode of AKI has been estimated to give an 8-fold chance of developing end stage renal failure and a 30-fold chance of developing chronic kidney disease (CKD).[4] The prevalence of chronic kidney disease ranges from 39-60% in heart failure cohorts and is associated with increased mortality and morbidity.[5, 6] Preventing AKI would save a considerable amount in addition to any subsequent CKD costs, estimated to be around £1.45 billion per year in the UK.[7]

Renal function can be overlooked due to lack of consensus on optimal timing and frequency of monitoring. NICE guidelines for management of chronic heart failure recommend a general rule of 6-monthly blood tests for urea and electrolytes in stable patients. However, renal deterioration can occur rapidly and unpredictably, and the guidance for monitoring in acute situations is unclear, often being at the discretion of the clinician on a case by case basis. Clearer guidance for monitoring renal function may be helpful in reducing admissions by facilitating earlier interventions such as modification of drugs and their doses which may be contributing to the renal decline. Development of such guidelines is needed in this particular patient group because many drugs used in the treatment of heart failure contribute to renal decline.[8]

This chapter is an overview of heart failure as well as the common medications used in its management, and how they relate to renal failure. Following this is an in-depth look at international guidelines for heart failure, focusing on frequency of renal monitoring in order to explore the evidence behind current practice.

1.2 Heart failure overview

To understand the relationship between the heart and the kidneys, it is essential to consider the role that the heart plays in normal physiology, and how that is changed by the heart failure disease process.

1.2.1 Heart failure physiology

The heart's function is always to supply the body with the amount of oxygen it requires. Heart failure is a failure of the heart to meet this function, through any number of disruptions to the heart's structure or compensatory mechanisms.

1.2.2 Pathophysiological causes of heart failure

The function of the heart relies on its specific size, valves, cardiac muscles, and rate of contraction, as well as compensation from the systemic blood vessels. These five elements can each be impacted negatively over time, causing the function of the heart to be impaired and leading to chronic heart failure. Each of these processes and their causes will be discussed in turn.

1.2.2.1 Size: Left ventricular end-diastolic volume (LVEDV)

The left ventricle (LV) receives oxygenised blood from the pulmonary vein and supplies blood via the aorta to the rest of the body. Therefore, in healthy patients, the volume of the LV at the end of diastole (LVEDV) is analogous to approximately the amount of blood that is pushed into the aorta in a single heartbeat. This is known as stroke volume (SV). The amount of blood that is passed through the heart per unit time, is the stroke volume multiplied by the heart rate (HR), which is known as cardiac output (CO = SV x HR). This is the measure by which we assess the body's demand, and thus the need for compensation. For example, during exercise, the body's demand increases to a point where a higher cardiac output is required. Therefore, the heart must increase its rate, so that the cardiac output can keep up with the increasing demand. However, the body is also able to increase the end diastolic volume via vasoconstriction of peripheral vessels to increase the pressure of the blood intravascularly, so that more blood rushes into the left ventricle during diastole, causing ventricular 'stretching'. This typically increases the end-diastolic left ventricular volume temporarily, and thereby increases stroke volume. Thus, during exercise, both SV and HR increase to provide the cardiac output needed. However, if a body is stressed over a prolonged period of time, such that the demand for oxygen always exceeds the heart's normal resting function, then these 'temporary compensatory mechanisms' are active all the time, which can be counter-productive over the long-term.[9]

The most common cause of heart failure is secondary to high blood pressure. As mentioned, an increased blood pressure raises the volume of blood entering the left ventricle during the short period of diastole. This volume of blood is known as pre-load, i.e. the load the heart takes on before it contracts. As this pre-load rises, the more pressure blood exerts on the inner wall of the left ventricle, causing it to stretch out to

accommodate the extra blood. When LVEDV expansion occurs over a prolonged period of time, it leads to re-structuring and permanent dilation of the LV. This dilation, along with compensatory increase in LV wall thickness, often leads to a much larger sized heart, known as cardiomegaly, a typical sign of chronic heart failure.[10] Once the LV reaches a certain diameter, the stroke volume begins to decrease due to the inability of the heart to contract fully. This is illustrated by the Frank-Starling curve (Figure 1.2), which shows that there is a plateau of contractility that is reached when the cardiac muscle fibres (sarcomeres) are stretched to their optimum length. Beyond this it becomes harder for the muscle to contract fully, leading to a dysfunction during systole, which is known as systolic heart failure. The implication of this is that not all of the blood is ejected from the left ventricle, so the output of the heart has dropped. The net effect is that the heart needs to find other ways to compensate for the increased demand for cardiac output, which in turn leads to an increase in heart rate and blood pressure. As the heart works harder to meet the demands of the body, this pressure-induced dilation worsens, and creates a negative cycle of muscle dysfunction, until the onset of heart failure.

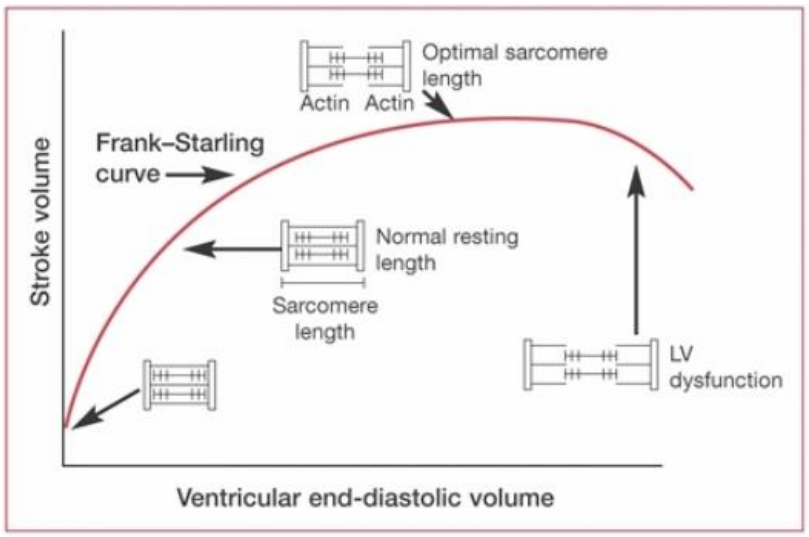

Figure 1.1 Frank-Starling Curve

Contractility of the left ventricle reaches a peak before becoming less efficient as LVEDV increases.[11]

The percentage of blood from the LV that is ejected during a single beat is measured as the left ventricular ejection fraction (LVEF). In the most common cases of heart failure, the diagnosis is reached by measuring LVEF by echocardiography. Once LVEF declines below 40%, the patient is diagnosed as having systolic heart failure.

The opposite mechanism can also lead to a reduction of cardiac output. If a pathology causes a decrease in the volume of the left ventricle, then it reduces the pre-load, and thereby reduces the stroke volume, leading to decreased cardiac output. This can happen in a number of ways. Pericardial diseases which cause fibrosis, such as constrictive pericarditis, can make the lining of the heart more rigid, and thus reduce the amount that the left ventricle is able to stretch to accommodate blood, resulting in less blood being ejected per beat.[12] Hypertrophic cardiomyopathy is a condition where the heart muscle walls thicken abnormally, resulting in reduced left ventricular volume due to over-thickening. This also leads to left ventricular outflow obstruction.[13] Finally, pulmonary embolism or pulmonary hypertension can also result in the right ventricle dilating abnormally and reducing the size of the left ventricle, reducing its output. In this way, an insufficient size of the left ventricle can cause compensatory changes that lead to chronic heart failure also.[14]

1.2.2.2 Valves and valvular disease

There are 4 main valves in the heart, two in each ventricle. When the ventricle contracts, it pushes blood outwards exerting a force in all directions. The valves therefore need to remain constantly functional at high pressures. If this function fails, and backflow occurs, as in valvular regurgitation, the amount of blood that is pumped forwards per beat is reduced, decreasing cardiac output, which then leads to other

compensatory mechanisms. The most common presentation of this is in the left ventricle where the pressures are highest, causing blood to push back against the mitral valve, leading to mitral regurgitation.

Some causes of acquired valvular disease include infective endocarditis, which can infect and degrade the leaflets themselves; degenerative, due to chronic high pressure changes to the valves; structural changes such as ventricular dilation; infarction, causing damage or death to the papillary muscles; and autoimmune diseases such as rheumatic fever that can affect the valves individually or cause fibrosis.[15]

Another mechanism by which valve function is disrupted is when the opening of the valve is too narrow. This is known as valve stenosis: this results in less blood being pumped out of the outflow valves. The most common presentation of this is in the left ventricle when blood flow to the aorta is restricted, which is called aortic stenosis. The most common cause of aortic stenosis is calcification of the valve due to degenerative changes.[16]

1.2.2.3 Cardiac muscle dysfunction

Dysfunction of the cardiac muscle is also an important cause of heart failure, since it reduces the strength and efficiency of each contraction. The most common cause of muscle dysfunction is myocardial ischaemia or infarction. Another important cause is pathology of the muscle known as cardiomyopathy, which directly reduces the strength of muscle contraction. Cardiac muscle can also develop inflammation, known as myocarditis, which can also affect muscular function.[17]

1.2.2.4 Rate and rhythm

Deviations from normal heart rhythm result in a reduced efficiency of each beat, causing a drop in cardiac output. An example is in atrial fibrillation, where the atrial muscles contract rapidly and sporadically, without co-ordination, which reduces the overall strength of atrial contraction and fails to coincide with the ventricular rhythm, which reduces LVEDV, and thus cardiac output. Other conditions which affect heart rhythm can also cause heart failure over time such as thyrotoxicosis, or secondary to right-coronary artery infarct.[18, 19]

1.2.2.5 Systemic vascular resistance

Compensatory mechanisms by way of vasoconstriction and vasodilation of the peripheral blood vessels can control the blood pressure which determines the preload. Pathologies which disrupt this mechanism can alter the cardiac output; for example, in the case of sepsis, there is widespread vasodilation, which reduces blood pressure, and can therefore lead to acute heart failure.[20] Pregnancy is another physiological state that can also alter vascular resistance and cause a similar change over a longer period of time.[21]

1.2.3 Characterisations of heart failure

Heart failure is defined as the inability of the heart to provide blood to meet the body's demands. While the most frequent cases involve systolic heart failure, there are other types that fit within the definition.

As a counterpoint to systolic, there is also diastolic heart failure, which is when the heart has a reduced ability to relax. This results in restricting the ventricular stretch when blood fills the left ventricle, leading to reduced stroke volume and reducing

cardiac output. Heart failure may also be defined as left-sided or right-sided, depending on which side has the most deficiency in function, which has different manifestations on the body.

Another classification is based on ejection fraction, i.e. reduced ejection fraction (LVEF <40%), or a preserved ejection fraction. The latter a relatively new classification and there is still debate as to its most common aetiologies. However, it encompasses all other causes of heart failure that do not actively reduce the ejection fraction of the heart, such as degenerative changes in the microvasculature which reduce systemic compensation.[22]

Furthermore, heart failure can also be characterised as either low output or high output. Systolic heart failure typically results in low output heart failure, which means that the functional output from the heart is reduced. High output heart failure is when the function of the heart is not impaired, but the demands of the body for blood may be increased such as in hyperthyroidism, or in anaemia.[23]

1.2.4 Clinical manifestations

1.2.4.1 Left sided heart failure

Symptoms from heart failure cause back-pressure on the blood vessels on the affected side. This essentially means that intravascular fluid is pushed out of these vessels causing oedema. If the left heart is affected, then this back pressure occurs in the pulmonary vessels, resulting in pulmonary oedema. This increases the demands of the body for oxygen and causes the compensation from the heart to increase, worsening heart failure further. The pulmonary fluid can cause a chronic cough productive of clear or red-tinged sputum, with associated shortness of breath, which gets worse with

exacerbations of the heart failure. More chronically, the reduction in oxygen saturation causes symptoms of dizziness, confusion, weakness, fatigue, or even syncope.[24]

1.2.4.2 Right sided heart failure

When the right side of the heart is affected, the back pressure affects all the vessels leading up to the vena cava, which drains blood from the peripheries and the rest of the body. This results in peripheral oedema mainly located around the ankles and sometimes the sacrum. This makes it difficult to mobilise, and also results in weight gain, since the loss of fluid into the sub-cutaneous space causes the kidneys to compensate and retain fluid into the body. The back pressure affects other organs also including the kidney, liver, spleen and peritoneum causing symptoms such as ascites, liver and spleen enlargement, and abdominal pain.[25]

Clinical signs of heart failure include low blood pressure, low pulse pressure and low volume pulse from the reduced cardiac output.[26] Reduced renal function and urine output are a result from reduced kidney perfusion.[27] Bibasal crepitations on auscultation are found due to the pulmonary oedema, leading to a high respiratory rate.[28-31]

1.2.5 Clinical management of chronic heart failure

The first line of treatment for early heart failure is conservative management through a combination of diet and lifestyle changes including reducing smoking and alcohol intake, weight loss, exercise, low salt diet and fluid restriction. Regular cardiac rehabilitation can help increase functional capacity of patients who normally feel fatigued. An annual influenza vaccination is also recommended to reduce the likelihood of exacerbation due to infection. Sometimes counselling or cognitive

therapy is advised for these patients as the chronic condition leads to an increased likelihood of depression and mental anxiety.

In managing the mechanisms and disease process of heart failure medically, there are 3 main strategies:

1) Relieve the pressure from the preload, to slow down remodelling and thus improve long-term prognosis
2) Symptomatic control
3) Reducing long-term risks from common causes of heart failure

1.2.5.1 Preventing remodelling and improving prognosis

Patients diagnosed with chronic heart failure are typically on a combination of medications which have been seen to improve the prognosis of heart failure. These include:

a) Either an ACE inhibitor (ACEi) or Angiotensin-receptor blocker (ARB) or a sacubatril/ valsartan combination therapy, or a hydralazine/isosorbide dinitrate combination therapy. Specific drug selection is based on patient tolerance to the drug and the severity of their symptoms.[32]
b) A beta blocker such as bisoprolol[33]
c) A mineralocorticoid antagonist such as spironolactone or eplerenone[34]

Each of these classes of drug are important for reducing the remodelling process and prolonging life expectancy of heart failure patients. While the precise mechanism of remodelling prevention is unclear, it is thought that the effects on the systemic circulation, especially on the renal vasculature, which promote vasodilation and reduce fluid retention, have a beneficial effect in reducing effective pre-load to the heart and thus preventing ventricular stretching and eventual remodelling.[35]

1.2.5.2 Symptomatic control

The most distressing and acutely damaging symptom is pulmonary oedema. This is often counteracted by diuretic agents such as furosemide, which is a loop diuretic. These work by promoting fluid loss via the kidneys. The circulating blood volume decreases, reducing intravascular pressure and thus the pulmonary oedema.[36]

For patients with palpitations and atrial fibrillation, rate controlling medication such as digoxin or ivabradine may be used. Digoxin in some patients may be useful for heart failure symptoms by both reducing the heart rate and also increasing the contractility of myocytes, causing more forceful contraction, aiding the ventricle in emptying from an overfilled state.[37]

1.2.5.3 Reducing long term risks

This includes a statin to reduce risk from hypercholesterolaemia, aspirin to reduce risk of coronary artery thrombosis, and supplementary iron if the patient is anaemic. If the patient has atrial fibrillation, they may also be given warfarin to reduce risk of stroke, or a NOAC (novel oral anticoagulant) in its stead. If a patient continues to have a raised blood pressure despite heart failure treatment, they can also be given a calcium channel blocker, such as amlodipine, to reduce their cardiovascular risk.[38]

1.3 Relationship between heart failure and renal failure

Heart failure itself is associated with high risk of renal dysfunction and chronic kidney disease (CKD).[39-41] Conversely, poor renal function has been shown to predict LV dysfunction.[42] This means that the onset of CKD is a risk factor for the subsequent development of heart failure.[43, 44] There is even evidence to suggest that estimated

glomerular filtration rate (eGFR) correlates strongly with LV function well before any diagnosis of renal failure or heart failure has been made.[45-47] Indeed, up to a quarter of patients with CKD have symptoms suggestive of heart failure prior to being diagnosed.[48] Collectively, the bidirectional link between cardiac and renal function can lead to clinical presentations that are termed cardio-renal syndrome (CRS).

There are five types of CRS, the classification of which reflects the presumed primary and secondary problem:[49]

- **Type 1**: Acute heart failure causes acute kidney injury
- **Type 2**: Chronic heart failure causes chronic kidney disease
- **Type 3**: Acute kidney injury or acute renal failure causes acute cardiac failure
- **Type 4**: Chronic kidney disease causes chronic cardiac dysfunction, including heart failure
- **Type 5**: An acute or chronic systemic disorder causes both cardiac and renal failure (e.g. sepsis, diabetes mellitus, SLE)

The mechanism of renal injury in CRS is not clear but is likely to be multifactorial. The interaction between heart and renal failure can be described in terms of heart failure pathophysiology, renal responsive changes and the drugs to which patients are exposed.

1.3.1 Heart failure pathophysiology causing renal decline

Heart failure states cause increased central venous pressure (CVP). This venous back pressure can be transmitted to the renal vasculature causing chronic renal venous

congestion, which in turn reduces glomerular blood flow by reducing the pressure gradient between afferent and efferent arterioles.[50] The observed association between high CVP states and fall in renal function is consistent with this paradigm.[51]

In addition, right ventricular (RV) dilation in heart failure (which increases CVP) lowers cardiac output by several mechanisms. Firstly, the direct effect of over-dilation causes decreased ventricular contractility via the Frank-Starling Relationship (Figure 1.2).[52] Secondly, dilation of the RV impairs LV filling by increasing LV extramural pressure, reducing LV functional volume and reducing preload (the reverse Bernheim phenomenon).[53] The resulting reduction in cardiac output decreases renal perfusion and measured renal function.

1.3.2 Structural and responsive renal changes during heart failure

Changes in renal perfusion are likely to account for much of the renal deterioration in patients with heart failure. However, the situation can be aggravated by drugs used to manage heart failure such as diuretics, which reduce intravascular volume and renal perfusion.[54] Compensatory mechanisms are activated to attempt to maintain intravascular pressure and preserve renal perfusion. Chronic compensation puts stress on normal regulatory systems increasing risk of progressive failure. An important mechanism is the renin-angiotensin-aldosterone (RAA) system. This is activated by low renal arteriolar pressure, causing secretion of angiotensin, which promotes vasoconstriction. It also upregulates the release of aldosterone, which promotes sodium retention.[55] Long-term activation of the RAA system is harmful, causing an increased risk of long-term renal impairment. The mechanism by which chronic RAA system activation causes harm is not clear, but contributing factors likely include systemic vasoconstriction. This increases cardiac afterload which is the pressure the

LV needs to overcome to push blood into the aorta. The higher the afterload, the harder the LV needs to work, which further hinders the cardiac output of a dilated heart. This leads to an even greater reduction in renal perfusion, causing further activation of the RAA system and a vicious cycle of deterioration.[56]

1.3.3 The effect of heart failure medication on renal function

Drugs used to manage heart failure can reduce renal function by various mechanisms. This is particularly relevant in CRS types 1 and 2 where heart failure leads to renal failure.

1.3.3.1 Loop Diuretics

These drugs promote natriuresis by reducing sodium reabsorption via the Na-K-Cl cotransporter (NKCC) in the loop of Henle, resulting in an efflux of water and reduction of intravascular volume. While this is beneficial for symptomatic heart failure with volume overload, it decreases total blood volume and thus reduces blood pressure contributing to renal hypoperfusion and compensatory systemic and renal vasoconstriction to maintain blood pressure. Since the function and perfusion of glomeruli rely on a constant flow from the renal arterioles, any reduction in flow in this way leads to renal decline, and if the patient's compensatory mechanisms fail, it can quickly deteriorate into AKI.[57]

1.3.3.2 Thiazide diuretics

These drugs inhibit the sodium-chloride transporter in the distal tubule. Their hypotensive effects may also be useful for achieving BP targets in patients with ischaemic heart disease (IHD) while the natriuretic effect can protect against

pulmonary oedema. The hypokalaemic effect can counter-balance the potassium raising effects of ACEi/ARBs and potassium-sparing diuretics.[58, 59] As with loop diuretics, renal function can deteriorate acutely as a consequence of the hypovolaemia, resulting in AKI, or gradual progression of CKD.[60, 61]

1.3.3.3 ACE inhibitors and ARBs

Many studies have shown a prognostic benefit of ACEi/ARBs in both heart failure and renal failure. Their effect on blocking the RAA system causes a predictable increase in serum creatinine because of their effect on intraglomerular haemodynamics. As serum creatinine currently remains the main biomarker for measuring renal filtration function, an acute decline in renal function might be apparent on initiation or dose escalation of these drugs. The extent of the rise in serum creatinine may indicate whether it is a physiological or pathological response, with a total rise of up to 20% generally considered acceptable. Combination of ACEi/ARBs with other 'high risk' medications and a background of pre-existing renal disease may cause subsequent renal deterioration, if not titrated appropriately.[62, 63]

1.3.3.4 Beta blockers

Bisoprolol is the most commonly used beta blocker in heart failure, and is known to improve prognosis,[64] probably through a combination of both sympathetic inactivation, resulting in downregulation of the RAA system, as well as reduction in endothelin-1 and thromboxane prostaglandins which promote vasoconstriction in response to sclerosis and injury. These effects result in renal arteriole vasodilation which improves blood flow and protects renal perfusion.[65] Renal decline can occur with beta-blockers due to a reduction in cardiac output, consequent to the bradycardia,

which could reduce renal perfusion.[66, 67] However, bisoprolol has largely been accepted as being safe over a long-term period in renal failure.[68, 69] Indeed it continues to be of prognostic benefit even in renal decline, and this benefit is even greater in patients with the most severe stages of renal failure, without affecting overall eGFR significantly.[70]

1.3.3.5 Aspirin

This is commonly used in secondary prevention of ischaemic heart disease because of its anti-platelet effects. Rarely aspirin can cause an idiosyncratic reaction causing tubulointerstitial nephritis (TIN), which can lead to AKI. This is rare at low doses of 75mg/day, although the risk is slightly higher if combined with other NSAIDs and analgesics.[71] Similar to other NSAIDs, aspirin at high doses can be nephrotoxic because of detrimental effects on renal prostaglandins. It can also cause fluid retention, which can exacerbate heart failure.[72]

1.3.3.6 Calcium channel blockers

Heart failure patients often suffer from hypertension, especially if the primary cause is due to ischaemic heart disease. These patients are likely to be prescribed hypotensive agents such as calcium channel blockers. By reducing systemic blood pressure, these agents may also carry a potential risk of reducing perfusion and filtration pressure through the kidney, causing renal ischaemia and decline in function over time.[73] However, in practice, amlodipine seems to have renoprotective effects in CKD patients, especially when paired with ARB blockers.[74, 75] This is probably due to a reduction in renal artery smooth muscle contraction leading to a higher renal flow,

even while systemic blood pressure is reduced.[76] Indeed, even a single dose of amlodipine can lead to a demonstrable increase in eGFR in CKD patients.[77]

1.3.3.7 Aldosterone antagonists

Spironolactone and eplerenone have shown significant benefit in heart failure outcomes, but they can also lead to serious adverse effects. As with loop and thiazide diuretics, they can increase risk of dehydration and hypoperfusion. They also cause potassium retention which can lead to hyperkalaemia, the risk being higher in CKD. Hyperkalaemia increases risk of arrhythmias, morbidity and mortality. Concurrent use of aldosterone antagonists with ACEi increase risk of hyperkalaemia and so should be used with caution.[39]

1.3.3.8 Digoxin

This is now used infrequently in patients with heart failure, and is used mainly in patients with concomitant atrial fibrillation. Digoxin has positive inotropic and negative chronotropic effects. There have been very few studies of the effects of digoxin on renal function in patients with heart failure and CKD, but it seems to have minimal effect on renal function in small doses. Conversely, since digoxin excretion is mainly renal, accumulation can occur in severe kidney dysfunction, leading to digoxin toxicity and potentially cardiac arrhythmias.[61]

1.3.3.9 Hydralazine and Nitrates

These drugs both increase nitric oxide (NO) availability in blood. NO is a potent vasodilator of systemic vasculature which lowers blood pressure and potentially increases renal arterial flow. This effect has been demonstrated during intravenous

administration in an acute setting.[78] Isosorbide dinitrate (ISDN) combined with hydralazine has been shown to decrease mortality in patients with renal failure.[79] Hydralazine can rarely cause drug-induced lupus, which can also lead to renal dysfunction.[80] Hydralazine is also renally excreted and can accumulate in patients with CKD.[81]

1.3.3.10 Ivabradine

This is used to reduce heart rate in patients already taking beta blockers, who remain symptomatic. This drug acts on the sinoatrial node to delay repolarisation. Only 20% of ivabradine is renally excreted, with no known associations with renal pathology making it unlikely to pose a renal risk.[64]

1.3.4 The biomarker manifestations of renal decompensation

During a period of renal decline it can be observed that a patient's biomarkers most commonly develop an increase in serum creatinine as well as serum urea levels. Creatinine is a waste product from degrading muscle and other proteins in the body, and is filtered out via glomerular excretion of the kidneys. The rate at which it is cleared is therefore proportional to the amount of functioning glomeruli in the patient. Therefore if there is acute impairment in kidney function, creatinine levels rise sharply.[82] Similarly, serum urea is the result of breakdown products from dietary and cellular protein, which are also excreted via glomerular filtration. Much like creatinine, it is filtered out in proportion to the cellular function of the kidney and glomerular apparatus. High urea is also correlated with dehydration which is a renal risk factor.[83] In clinical practice, creatinine and urea trends are often used to determine the overall trajectory of renal decline.[84]

Acute kidney injury (AKI) is a rapid deterioration in renal function, usually over days to weeks. It is defined arbitrarily by a rise in serum creatinine or a fall in urine output, according to internationally accepted criteria such as the Kidney Disease Improving Global Outcomes (KDIGO) classification. AKI is defined as an increase in serum creatinine by 50% from baseline within 7 days, or an absolute increase in creatinine by 26.5 µmol/l over 48 hours, or the presence of acute oliguria (<0.5 ml/kg/h for 6 hours).[85] It is then staged (1-3) by further specific creatinine or urine output criteria. AKI is a common cause of hospital admission for patients with heart failure. In many cases the development of AKI, or increase in its severity, may be preventable with appropriate monitoring of renal function and adjustment of prescribed drugs. Earlier detection of AKI by laboratory or clinical parameters allows earlier intervention and increased chance of prevention or amelioration.

One early warning system is the clinical classification of Worsening Renal Function (WRF). WRF is a state of pre-AKI which is specific to heart failure patients. It has a more gradual biomarker (creatinine) increase than AKI, occurring over 6-12 months rather than 7 days, which makes it easier to detect in the community than the criteria for AKI.[86] WRF is associated with greater mortality, morbidity and hospitalisation rate attributable to both renal decline and heart failure. WRF acts as an early warning system for progression of renal impairment, and allows for earlier intervention so that hospital admission can be avoided.[87] There are various definitions of WRF described in the literature, generally accepted ones being: either 25% increase in baseline creatinine; 26.5 µmol/l absolute increase in creatinine; or 20% decrease in eGFR. While these criteria are similar to the AKI definition, the difference is the much longer timescale. More recently, WRF has been divided into 3 classes based on severity of renal decline (Table 1.1).[56]

Table 1.1 WRF categories vs AKI

The accepted biomarker definitions of worsening renal function (WRF) classes compared to Kidney Disease Improving Global Outcomes (KDIGO) Acute Kidney Injury (AKI) definition[85, 88]

Clinical criteria	**WRF Class I**	**WRF Class II**	**WRF Class III**	**AKI**
% creatinine increase		25%		50% (over 7 days)
Raw creatinine increase (µmol/l)	17.7 – 26.5	26.5 – 44.2	>44.2	>26.5 (over 48 hrs)
Raw eGFR decrease (ml/min/1.73m^2)	5 - 11	11 - 15	>15	-
% eGFR decrease	-	20%	-	-
Timescale	6–12 months	6–12 months	6–12 months	7 days/48 hrs

The definition of WRF relies on biomarker change from an established baseline, which can be measured either as a percentage decrease in eGFR, raw decrease in eGFR, or raw increase in serum creatinine.[89] Therefore true risk of renal decline must take into account baseline renal function which is most commonly defined using eGFR formulae (Table 1.2).[90, 91] This, in turn, influences their risk of further deterioration.[92] CKD is graded from G1 (Normal) to G5 (End-stage renal failure), the greater the severity, the greater the risk of mortality from any cause, cardiovascular events and hospitalisation.[93]

Table 1.2 Grading of CKD based on KDIGO eGFR CKD definition[93]

eGFR category	eGFR (ml/min/1.73m^2)	Renal function
G1	>89	Normal or High
G2	60-89	Mildly decreased
G3a	45-59	Mild – moderate decrease
G3b	30-44	Moderate – severe decrease
G4	15-29	Severely decreased
G5	<15	Kidney failure

As heart failure progresses in patients, it is often accompanied by progressive CKD with a fall in eGFR.[41] The patient is then at increased risk of WRF and subsequent AKI. This risk is usually compounded by the various drugs and systemic insults to which patients with heart failure are often exposed.[39, 94] An effective system of regular monitoring can help clinicians intervene at a stage sufficiently early to reduce risk of progression to kidney failure.

1.4 Methods of review

The following databases were searched for clinical guidelines for heart failure and studies of renal monitoring in heart failure: Cochrane Database of Systematic Reviews (CSDR), Database of Abstracts of Reviews of Effects (DARE), Cochrane Central Database of Controlled Trials (CENTRAL), MEDLINE, EMBASE, Web of Science and CINAHL. Studies of interest were further reviewed for inclusion of heart failure guidance. Selection of clinical guidelines was agreed by consensus of clinical

investigators for relevance to this review. Cited studies within these publications were scrutinised. Only English studies were included in this review. Search strategy for other related references can be found in Appendix 1.

1.5 Renal function monitoring in current guidelines for chronic heart failure

1.5.1 Frequency of renal monitoring

No study has specifically assessed frequency and optimal timing of renal function monitoring with respect to clinical outcomes in patients with heart failure. Various studies have emphasised the importance of frequent and regular monitoring of renal function but there is no evidence-based gold standard.[88, 95]

To address optimal frequency, published heart failure management guidelines were be reviewed. Other relevant factors were then taken into account such as renal pharmacodynamics, rate of renal decline, risk factors for renal decompensation and the time required for an intervention to have an effect.

1.5.2 NICE guidelines for chronic heart failure in adults

The National Institute for Health and Care Excellence (NICE) clinical guidelines for the management of chronic heart failure (Oct 2014)[1] advises a minimum frequency of 6-monthly monitoring for patients with stable CHF. Increased frequency (of "days to 2 weeks") is recommended if changes are made to the drug regimen. More detailed monitoring is suggested for patients with "significant comorbidities or deterioration" though this is not elaborated on further. These are relatively non-specific monitoring recommendations open to interpretation by clinicians.

For ACEi and ARBs more specific guidance exists. Checking baseline renal function on initiation of the drug is recommended, with dose titration 2-weekly, monitoring renal function each time until target dose is reached. Cross-referencing to NICE clinical guidelines for chronic kidney disease, renal function monitoring is advised 1-2 weeks after initiation or dose increment. Regular follow-up monitoring of renal function is advised every 3 months if the patient continues to take ACEi or ARBs. The guidance advises against use of these medications with baseline potassium >5 mmol/L and recommends discontinuation at ≥6 mmol/L. Maximum permitted fall in renal function after ACEi/ARBs initiation or titration is suggested to be 25% decrease in eGFR or 30% increase in creatinine from pre-treatment levels. ACEi or ARB dose should be reduced or the drug discontinued if these limits are exceeded. Any lesser degree of renal deterioration warrants further testing after 1-2 weeks, but the dose should not be decreased unless these limits are exceeded.

The risk of hyperkalaemia with aldosterone antagonists is emphasised with renal function tests suggested post-initiation at 1 week, then at 1, 2, 3, 6 months and then 6-monthly if stable. Dose should be halved if potassium reaches 5.5-5.9 mmol/L and stopped if it reaches 6 mmol/L. The guidance also advises frequent monitoring in patients taking loop and thiazide diuretics alongside aldosterone antagonists, as well as advising monitoring of potassium when digoxin is prescribed concurrently, but no frequency is specified.

In summary, the minimum monitoring frequency recommended by NICE is 6-monthly unless the patient's condition or medication has changed, in which case the minimum interval is reduced to 2 weeks but can be more frequent at the discretion of the clinician. The rationale is that medication for heart failure can cause adverse effects such as dehydration and renal impairment that can manifest within 2 weeks. These recommendations were based on analyses of local data looking at incidence of renal

impairment, hospital admission, re-admission and length of stay in patients where medication had been changed.[1]

Evidence used for these suggestions included a study from 1995 in which spironolactone added to ACEi and diuretics resulted in 4/28 patients having a significant rise in creatinine and hyperkalaemia. These changes occurred by first follow up at 4 weeks and were asymptomatic. Therefore this study recommended weekly monitoring of renal function during initiation and titration of aldosterone antagonists for all patients. [96]

Management and monitoring of ACEi, ARBs, beta-blockers and spironolactone in CHF were also addressed by McMurray and colleagues.[97] Their recommendations were based on expert opinion and clinical safety trials published before 2001. These recommendations were adapted by the NICE Guideline Development Group and further updated in 2010 using evidence from NICE clinical guidance on management of chronic kidney disease.

1.5.3 SIGN guideline on management of chronic heart failure

The Scottish Intercollegiate Guidelines Network guideline on management of chronic heart failure (March 2016)[98] also advises on monitoring of renal function in CHF. For ACEi and ARBs, renal function and electrolyte monitoring is recommended 1-2 weeks after initiation or dose increase. Renal function should then be monitored "frequently and serially until potassium and creatinine have plateaued", but no specific frequency is suggested.

Maximum acceptable increase in creatinine after ACEi or ARB introduction is considered to be 50% or 266µmol/L from baseline with a maximum acceptable serum potassium of 5.5 mmol/L. If these limits are reached, other 'high risk' agents should

be reviewed and discontinued first. If renal function does not improve, ACEi or ARB dose should be halved before re-checking renal function after 1-2 weeks. If there is still no improvement, specialist opinion should be sought. At no point is there a recommendation to stop ACEi/ARBs and the only contraindications mentioned are angioedema and bilateral renal artery stenosis.

For beta-blockers, renal function monitoring is also recommended 1-2 weeks after initiation or dose change. Dose should be reviewed in the event of hypotension, bradycardia, or fatigue but renal dysfunction is not specifically mentioned.

Guidance regarding aldosterone antagonists is, as with NICE, more comprehensive due to the increased risk of hyperkalaemia. The recommendation is similar to that of NICE with renal function testing at 1 week, then at 2, 3, 4, 6 months then 6-monthly thereafter if stable. Dose should be halved with serum potassium of 5.5 mmol/L or above and stopped if above 6 mmol/L. Monitoring with loop diuretics is mentioned but no specific time interval suggested.[98]

It is worth noting that this SIGN guidance is also derived from McMurray and colleagues'[99] practical recommendations for heart failure, the same source used by NICE but follows it more closely than does NICE. This is apparent in the quoted maximum acceptable creatinine rise before intervention is deemed necessary. NICE uses its own limit of 30% increase in creatinine compared with McMurray's (and SIGN's) 50% increase from baseline. It is clear from the wording of the publication by McMurray and colleagues that the higher threshold was designed to prioritise prescription of ACEi, ARBs, and cardiovascular outcomes in heart failure over that of the risk of renal decompensation.

1.5.4 ESC guidelines for the diagnosis and management of acute and chronic heart failure

The European Society of Cardiology guidelines for the diagnosis and management of acute and chronic heart failure (May 2016)[35] acknowledge the high prevalence of CKD in HF and the frequent onset of WRF as a risk factor for future morbidity, AKI and hospital admission. They advise caution when using thiazide and loop diuretics in the context of declining renal function, but they encourage continuation of ACEi and ARBs unless there is a "large decrease" in renal function as a result.

Supplementary information provides some drug-specific monitoring advice. For ACEi and ARBs, testing is advised 1-2 weeks after initiation and then 1-2 weeks after final titration only (which may be up to 5 dose titrations later). However, they note that blood chemistry should be monitored "frequently and serially until creatinine and potassium have plateaued". When stable, regular monitoring is suggested at 4-monthly intervals. Maximum accepted rise in creatinine is 50% or 266µmol/l from baseline. Deterioration above this level should trigger a review of other high-risk medicines followed by halving of the dose of ACEi or ARB with repeat renal function check after 1-2 weeks. ACEi and ARBs should be discontinued if creatinine increases by 100% or more, or 310 µmol/L or if eGFR drops below 20 ml/min/1.73m^2 or if potassium exceeds 5.5mmol/L.

For aldosterone antagonists, ESC advises renal function and electrolyte checks at baseline, 1 week, then 1, 2, 3, 6, 9 and 12 months after initiation, then 4-monthly when stable. For hyperkalaemia, they advise halving the dose at 5.5mmol/L and discontinuation at 6mmol/L.

For diuretics, ESC recommends renal monitoring at baseline, then 1-2 weeks after initiation or dose change. Discontinuation of diuretics is recommended in the event of worsening renal impairment or dehydration.

The ESC recommendations are based predominantly on expert opinion. No specific references are given with respect to renal monitoring, although they are similar to NICE and SIGN guidelines (Table 1.3).

1.5.5 ACCF/AHA guideline for the management of heart failure

The ACCF/AHA guideline for the management of heart failure (October 2013)[100] describes a more pragmatic approach to diuretic prescribing. It is suggested that furosemide, the most common diuretic in HF, is titrated up based on daily weight of the patient to achieve daily weight loss of 0.5-1.0 kg, followed by a lower maintenance dose to keep weight at the target. The dose can then be adjusted in primary care or by the patient, as necessary, over the longer term. For ACEi and ARBs, advice is to start at a low dose then monitor renal function after 1-2 weeks then "periodically thereafter" according to the clinician's judgement, including after dose increases. Risks of renal decline in patients with diabetes and hypertension are noted.

For aldosterone antagonists, a more stringent monitoring regimen is advised, with the option of an alternate day starting dose for patients with CKD and monitoring after 2-3 days then at 7 days for all patients. Thereafter monthly monitoring is advised every 3 months if renal function is stable. This monitoring schedule should then be repeated every time the dose changes. Sources of this guideline included 9 trials involving ACEi, 6 relating to ARBs, 25 to diuretics and 5 to aldosterone antagonists. The guideline also cross-referenced ESC and NICE guidelines.

Compared with other guidelines, advice on renal monitoring is less specific though there is generally a more cautious approach with respect to the risk of worsening renal function. ACEi and ARB guidance is similar to other guidelines but a more cautious approach is adopted to aldosterone antagonists. This reflects the high risk of

hyperkalaemia observed in its referenced studies reaching up to 36% in certain population based registries and an associated increase in mortality.[101] These findings are supported by the UK national heart failure audit, which lists serum potassium >5.5 mmol/L as the main predictor for mortality in inpatients with heart failure.[2] This encourages a stricter schedule of electrolyte monitoring with aldosterone antagonist prescription, which is mirrored in this guideline.

Table 1.3 Summary of clinical guidelines relating to renal function monitoring in chronic heart failure

	NICE	**SIGN**	**ESC**	**ACCF/AHA**
Stable	6 monthly	Non-specific	Non-specific	Non-specific
Clinical deterioration	Days – 2 weeks	1-2 weeks	Non-specific	Non-specific
Change in medications	Days – 2 weeks	1-2 weeks	Non-specific	Non-specific
Digoxin	Non-specific	Not mentioned	Non-specific	Non-specific
Aldosterone antagonist	1 week, then 1, 2, 3, 6 months, then 6 monthly if stable	1 week, then 1, 2, 3, 6 months, then 6 monthly if stable	1 week, then 1, 2, 3, 6, 9, 12 months, then 4 monthly if stable	2-3 days, 7 days, then monthly for 3 months, then 3 monthly if stable
ACEi/ARBs	At initiation, 2 weeks, then every 3 months when stable, every dose change	1-2 weeks after initiation or dose change	1-2 weeks after initiation and 1-2 weeks after final dose titration, then 4 monthly when stable	1-2 weeks after initiation or dose change
Threshold for reviewing ACEi/ARBs or aldosterone antagonist	Creatinine: >30% increase eGFR: >25% decrease	Creatinine: >50% increase or >266umol absolute increase Potassium: >5.5 mmol/L	Creatinine: >50% increase or >266umol absolute increase Potassium: >5.5 mmol/L	Development of WRF (Creatinine >25% increase) Potassium: >5.5 mmol/L
Loop Diuretic	Non-specific	Non-specific	At initiation, then 1-2 weeks after initiation and each dose change	Non-specific
Thiazide diuretic	Non-specific	Non-specific	At initiation, then 1-2 weeks after initiation and each dose change	Non-specific
Hypotensives (beta blockers)	Not mentioned	1-2 weeks after initiation or dose change	Not mentioned	Not mentioned
CKD + ARB/ACEi	At initiation, 1 week, 2 weeks, and at dose changes	Non-specific	Non-specific	Non-specific

1.5.6 Heart failure medications: renal effects and monitoring according to guidelines

1.5.6.1 Diuretics

Despite widely acknowledged potential detrimental effects of loop and thiazide diuretics on renal function, only the ESC guidelines provide specific monitoring advice regarding their use in heart failure. This contrasts with guidance regarding aldosterone antagonists, which is comprehensive and specific in each guideline, reflecting evidence for risk of hyperkalaemia, which is a predictor of mortality.[102, 103] Furthermore, prolonged use of spironolactone in patients with heart failure can increase risk of developing CKD, leading to this potassium-sensitive state much sooner.[39] Stringent monitoring systems are therefore justified for this drug class.

With loop diuretics, the risks may actually be at least as great as with aldosterone antagonists. In patients with heart failure, use of loop diuretics is associated with more severe renal decline, higher risk of hospital admission and increased mortality rate. The renal decline is dose-dependent with higher doses causing more rapid decline in eGFR.[39, 104] This association is increased in patients with WRF, causing even greater risk of mortality and dose-dependent renal decline.[105] It is not surprising then that increased use and requirement for both loop and thiazide diuretics are associated with increased risk of end-stage renal disease.[39, 106]

Paucity of renal function monitoring guidance for loop and thiazide diuretics, compared with aldosterone antagonists, likely relates to the fact that trials of the latter were conducted relatively recently. Lack of guidance for renal monitoring with diuretics may partially explain why diuretics are the second most common cause for U.K. hospital admissions due to adverse drug reactions.[8] If patients at highest risk of renal decline are given the highest doses, without specific monitoring advice, poor

outcomes are not surprising. These risks should be emphasised as much for diuretics as for aldosterone antagonists, in current guidelines.

Pharmacokinetic studies show that different diuretic agents have different durations of action in patients with heart failure, with different times from initiation to observed pharmacological effect (Table 1.4). Studies looking at the timed response to the loop diuretic bumetanide have shown that its diuretic effect occurs less than one hour after oral administration. Maximal effect is achieved after the first dose, with diminishing effect of subsequent oral doses (up to 25% less than the first dose for the same concentration).[107] These findings are supported by observed actions of the loop diuretic furosemide, which shows a maximal effect within 1.5 hours of the first oral dose and reduced effect with the same dose given repeatedly.[108] Of note, there are bioavailability differences between bumetanide (80%)[109] and furosemide (26-65%)[110] which can impact drug choice in clinical settings. For instance, a patient that fails to relieve symptoms with furosemide due to reduced absorption may still benefit more from oral bumetanide therapy without resorting to IV diuretics.

A similar effect has been seen with the thiazide diuretic hydrochlorothiazide.[111] The greatest diuretic effect is seen with the first few doses, causing significant electrolyte shifts within the first 3 days of administration. This can lead to hypokalaemia, hyponatraemia and compensatory mechanisms for sodium retention, including aldosterone release, thus effectively counteracting the diuretic effect. A new steady state is achieved after about 2 weeks where salt intake and natriuresis are balanced.

Table 1.4 Duration of action of diuretic agents used in heart failure[100]

Loop Diuretics	**Maximum Daily Dose**	**Duration of action**
Bumetanide	10 mg	4 – 6 h
Furosemide	600 mg	6 – 8 h
Torasemide	200 mg	12 – 16 h
Thiazide Diuretics	**Maximum Daily Dose**	**Duration of action**
Chlorothiazide	1000 mg	6 – 12 h
Chlorthalidone	100 mg	24 – 72 h
Hydrochlorothiazide	200 mg	6 – 12 h
Indapamide	5 mg	36 h
Metolazone	20 mg	12 – 24 h

These observations have implications for both diuretic dosing and monitoring of renal function. The greatest change in renal function biomarkers (such as serum creatinine) would be expected after the first dose and higher subsequent doses of the drug may be required for the same effect. In a patient with symptomatic heart failure, this may result in a progressive increase in diuretic dose with an accompanying greater risk of decline in renal function and AKI. This is compounded by the need for increasing doses of thiazide and loop diuretics as GFR falls.[93, 108] With reduced kidney perfusion, there is reduced rate of excretion of diuretic into the renal tubules which is required for these drugs to reach their sites of action. In addition, progressive nephron loss in CKD results in fewer sites at which the diuretics can act.[54] This not only reduces their effect as diuretics but also increases half-life in CKD, which can cause 'resistance' to the diuretic so that increasing doses are required over time.[112] In addition, bioavailability of oral diuretics may be reduced in patients with heart failure because of the presence of gut wall oedema.[108] So patients with CKD and symptomatic fluid

overload are faced with the highest initial risk of renal deterioration which is further increased by their need for higher doses of diuretics. Often this leads to hospital admission for administration of IV diuretics.

No simple monitoring schedule is applicable for any one class of diuretic. Patient and drug factors are both important, with consideration of both the acute and maintenance phases of the diuretic action. A regimen of 1-2 weeks' monitoring (recommended by ESC) may reach the steady state effect of the diuretic, but it does not take account of the risk of chronic slow deterioration in renal function. As discussed, monitoring of adequate frequency and duration is not reflected in current guidelines from NICE, SIGN and AHA, which rely predominantly on clinician judgement.

1.5.6.2 ACEi, ARBs and anti-hypertensives

The effects of ACEi and ARBs on renal function are well documented [87] and current heart failure guidelines emphasise the importance of renal function monitoring, suggesting no more than 2 weeks between initiation and first follow-up test. Slow titration is recommended at 2-week intervals with close follow-up after dose changes. This strategy facilitates detection of a sudden fall in renal function after drug initiation or a progressive deterioration with dose increments. Higher doses of ACEi are associated with risk of greater acute rises in creatinine over the first 4 months of therapy so relatively frequent monitoring is justified over this period.[113] Some studies advocate monitoring within 3-7 days of initiation of ACEi, to capture the first dose effect. This may be particularly relevant in patients with CKD (or transiently impaired renal function) and high baseline serum potassium, where there is relatively high risk of hyperkalaemia which can increase risk of mortality.[114] For this reason, the guidelines do advise caution for such patients. While the monitoring advice during

the titration period is appropriate, the risks of first dose effects could be better observed with earlier follow up after initiation such as post-first dose monitoring.

For beta-blockers and other anti-hypertensives which may be used in heart failure, only SIGN provides specific advice on renal monitoring. Other guidelines discuss symptomatic side-effects of beta blockade such as dizziness, fatigue and hypotension but do not advise specifically on monitoring of renal function. This demonstrates one of the problems of a predominantly 'medication-based' prescribing (and monitoring) approach in a complex condition such as heart failure.

1.6 'Medication-based' versus 'Patient-based' monitoring

The approach of current heart failure guidelines to renal function monitoring can be described as 'medication-based'. With scarcity of evidence, much of the guidance reflects expert opinion or adverse effect data from clinical trials. No studies have specifically addressed optimal timing of renal function monitoring, which has contributed to the potentially confusing variation in the published medication-based guidance.

For example, if a patient is taking a stable dose of spironolactone and then starts an ACEi, causing serum potassium to increase to 5.6, SIGN, ESC and ACCF would recommend halving of the spironolactone dose rather than review of the ACEi, even though the temporal relationship might suggest that the ACEi was the main adverse factor for this individual patient.

Linking monitoring guidance to individual drug classes disassociates it from the patient, so that if one particular drug is discontinued, the guidance is assumed to stop with it. This creates the danger that the role of the heart failure pathology itself in causing renal deterioration will be ignored. Monitoring may become more concerned

with detection of adverse effects rather than detection and reduction of progressive decline in renal function. This is reflected in current guidance for patients with apparently stable renal function, where only NICE has specific advice (of 6-monthly testing). This does not take account of individual patient risk factors such as age and co-morbidities.

In addition, guideline development is complicated by the fact that most patients with heart failure are prescribed multiple drugs (ACEi, spironolactone, loop diuretics, beta blocker etc.). Few studies have addressed the effect of such complex combinations on renal function in the medium-long term. For those studies that have, exclusion criteria might render the conclusions inapplicable to many patients with co-morbidities.

To rationalise guidance for monitoring of renal function and to minimise risk of WRF and AKI in vulnerable patients, a 'patient-based' monitoring regimen should be developed. This would consider both medication and individual risk factors, and suggest a monitoring interval based on a patient's combined risk, facilitating early intervention (such as dose adjustment) to reduce risk of renal deterioration, hospital admission and mortality.

1.6.1 Limitations of monitoring renal function

Serum creatinine has, for decades, remained by far the most widely used assay for measuring renal function in primary and secondary care. It is a product of normal striated muscle turnover and is a marker of renal filtration function rather than of acute renal damage, because to a large extent it is filtered freely by the glomerulus. Despite the longevity of this assay, creatinine is far from ideal as a marker of renal function. Firstly it does not increase linearly with fall in GFR; indeed GFR can fall significantly below normal with little or no increase in serum creatinine. Secondly, it is also

inaccurate at low GFR because the small degree of active tubular secretion of creatinine can confound the serum level. Conversely, drugs such as trimethoprim can cause spuriously high serum creatinine by blocking its tubular secretion. Thirdly, creatinine is a particularly poor marker of renal function at extremes of muscle mass. A serum creatinine of 130 µmol/L might represent normal GFR in a young person with high muscle mass or very low GFR in an older malnourished person.

It is also essential to understand that, while increase in serum creatinine over time suggests deterioration in renal function (and defines AKI and its stages), it does not provide any information on the underlying renal pathology. To take contrasting examples, a 50% increase in creatinine from baseline might result from dehydration, with no histological changes, or it might result (albeit rarely) from an intrinsic renal pathology such as glomerulonephritis. Clearly the clinician needs to apply clinical context and common sense to interpretation of the creatinine result.

Estimated GFR (eGFR) is derived from serum creatinine using formulae which include age, gender and ethnicity. Different formulae are described, the most commonly used being MDRD and CKD-EPI. A key point about use of eGFR is that it was developed and validated in populations with steady or slowly declining renal function. It is valid to use eGFR to monitor renal function over months and years, but for more acute changes in renal function, serum creatinine should be used.

In monitoring renal function in the context of initiation and titration of drugs, often the trend in creatinine (or eGFR over months) is more important than the absolute value. A serum creatinine rising from 100 µmol/L to 200 µmol/L over 6 months following introduction and titration of a drug is likely to be of greater concern than a serum creatinine that has remained stable at 220 µmol/L over the same period.

1.6.2 Clinical factors which impact WRF

Personal risk factors other than medication need to be considered for effective patient-based monitoring. These include gender, age, smoking status and co-morbidities such as diabetes and CKD.[56] By combining demographic factors such as gender and ethnicity with clinical history and co-morbidities, risk can be assessed more comprehensively than by considering only the drug regimen. Decision rules have not been developed for patients in the community with heart failure presumably because of the complexity of dealing with multiple risk factors. The lack of data from sufficiently large cohorts has also been a limiting factor, but may be easier with increasing adoption of electronic patient records.

1.6.3 Rate of renal decline

Rate of renal decline is itself a risk factor for further renal deterioration. Serum creatinine results inevitably fluctuate in patients with heart failure, often because of changes in their cardiac condition and associated changes in their drug regimen. Co-morbidities and other acute illnesses may also contribute to variation of creatinine between time points. However, the underlying or 'baseline' renal function nearly always declines over years, as is the natural history of most aetiologies of CKD. The average annual fall in eGFR over 4 years can be used as a measure of the rate of long term decline,[95] and can act as a prognostic indicator for both the heart failure and the renal outcome. For example, a rapid decline in baseline renal function is associated with increased risk of incident heart failure, before the diagnosis of heart disease.[115, 116] Furthermore, patients with higher rate of renal decline have higher risk of mortality associated with heart failure compared with those with a slower renal decline.[117, 118] There might therefore be some benefit in standardisation of this rate of decline, to facilitate risk stratification.

1.6.4 Timing of intervention (intervention lag)

This is the time taken from initiation of monitoring of renal function to a change in clinical management to avoid an undesirable outcome. Typically, this would simply involve the time taken for a patient to come back to clinic for a blood test, the waiting time for the result and the subsequent action which might involve another clinic visit or telephone call. In primary care this can be time consuming, especially if it relies on transportation of blood samples to a hospital laboratory. With further time for patient recall, the intervention lag could range from 2 – 5 days. The delay could be reduced with telephone follow up and use of recent advances in telemonitoring of clinical symptoms and signs.[119] Taking this intervention lag into account is essential in planning a monitoring schedule.

1.6.5 Personalised monitoring guidance – a new perspective

By incorporating a patient's drug regimen, personal risk factors, baseline renal function and time required to intervene, a flexible monitoring system could be developed to improve renal outcomes in patients at high risk. Simply increasing frequency of renal monitoring for all patients with heart failure would have significant cost implications and would also necessitate patients having to travel to GPs more frequently. Identification of patients at greatest risk of renal decline together with more efficient monitoring systems is likely to be the most cost-effective way of improving outcomes including hospital admission.

This type of personalised care requires an automated system to analyse individual risk factors and derive clinical guidance for each patient. This could be aided by recent advances in machine learning and virtual-intelligence-aided clinical-decision-tools,

which allow both rapid and intelligent assessment of biomarkers for clinical use.[120] For example, predictive analytics may be able to identify trends in eGFR and predict onset of WRF, calculating optimal monitoring time intervals and advising on dose adjustments to protect renal function. This personalised monitoring would take into account both early effects of medication changes and chronic effects of the disease process. Since it would be based on the individual patient, it would use cumulative data to improve its predictive accuracy with time.[121] Advances in remote care will help by bridging the gap between patient and clinician. This concept can be illustrated by the current work being developed by Google Deepmind's 'Stream' application, which collates hospital data from numerous sources, and uses predictive analytics to identify patients at highest risk of deterioration, allowing early intervention to avoid AKI in hospital inpatients.[122] Allowing frequent monitoring of renal function and instant medical feedback in this way would result in safer drug prescribing and lower risk of renal complications.[123]

In summary, renal dysfunction contributes substantially to morbidity and mortality in patients with heart failure and should be targeted to prevent deterioration in these patients over the longer term.[124] Current national and international CHF guidelines on renal function monitoring focus on drugs and their potential adverse effects, but offer less specific advice about monitoring of renal function in and of itself. This reflects a paucity of data from adequately powered clinical studies. Risk factors for deterioration of renal function in CHF have been identified and could be incorporated into a 'patient-based' approach to monitoring such as personalised guidelines based on predictive analytics.

1.7 Aims of the thesis

This introductory review of the current guidelines in practice has highlighted the changes that are required for safer monitoring. The PERMIT project (Personalised Renal Function Monitoring via Information Technology) is a series of studies and endeavours aimed at working towards these much needed 'patient-based' guidelines for renal monitoring in heart failure patients. It aims to utilise predictive analytics on large retrospective clinical datasets to create a prediction model for renal decline, personalised for each patient. This could then be used as the foundation for future clinical decision systems, such as personalised renal function monitoring for heart failure. Such guidance would use the predictive algorithm from this study to create clinical suggestions based on the unique predictions generated for each patient. This work falls in line with the NHS Long Term Plan to provide better access to decision support for clinicians and promote care plans using AI and predictive techniques to improve patient outcomes.[125]

It is envisioned that, in the future, this algorithm will be paired with remote care devices in the community such as point-of-care renal testing at home or at a local pharmacy; hence, work needs to be done into the way patients and clinicians interact with the medical technology devices that may facilitate remote monitoring. Therefore, the following two chapters address the future of medical technological advances in remote care for heart failure patients. Chapter 2 is a qualitative systematic review that examines how patients and healthcare staff engage with remote care. Chapter 3 adapts the high-level themes from the qualitative systematic review into a prospective patient-based questionnaire to ascertain the value respondents attribute to specific characteristics of remote care technology.

Chapter 4 describes the methods used to obtain the large clinical datasets, and the process used to prepare these data for analysis. Chapter 4 describes the patient dataset

obtained, in an epidemiological manner, to better assess the patient population on which the predictive algorithm will be based. Chapter 5 presents the machine-learning methods and outputs that led to generation of the predictive model.

CHAPTER 2

FACTORS AFFECTING PATIENT AND PHYSICIAN ENGAGEMENT IN REMOTE HEALTHCARE FOR HEART FAILURE: A SYSTEMATIC REVIEW

CHAPTER 2: FACTORS AFFECTING PATIENT AND PHYSICIAN ENGAGEMENT IN REMOTE HEALTHCARE FOR HEART FAILURE: A SYSTEMATIC REVIEW

2.1 Background

As mentioned in Chapter 1, heart failure patients are a vulnerable elderly patient cohort. They have reduced mobility, cognition, mood and often have 3-5 severe co-morbidities including diabetes mellitus, COPD, and ischaemic heart disease.[3] One year mortality rates for these patients are as high as 40%, and 30-50% of these patients are re-admitted to hospital each year due to worsening of the disease condition.[2] Self-care and efficacy issues prevail in the management of these patients, compounded by aspects of other co-morbidities as well as the complex nature of their management. The disease process in heart failure often leads to pulmonary and peripheral oedema which reduces patient mobility, and increases shortness of breath on exertion. The polypharmacy these patients are exposed to often mean that they are dealing with numerous side effects that can affect their day-to-day living and reduce their independence, such as by increasing their risk of falls.[126] Given the aging population with multiple comorbidities, it may be difficult to monitor patients' condition regularly in the community if they require frequent support and check-ups, since the reduced mobility and independence can impair access to health services.

Remote care technologies thus have the potential to benefit these patients by aiding self-care behaviours, and providing regular monitoring, bridging the gap between clinical visits.[127] Remote care technologies allow clinical care to be brought closer to the patient, which helps by allowing more frequent observations to occur in the patient's home and giving them access to greater tools for self-care.[128] In the long-term, the introduction of personalised, community-based technology may reduce the burden of healthcare appointments and increase effective management of symptoms, both in the community and via self-management.

Empowering patient self-management has the potential to identify any health issues early, providing an opportunity for intervention and thereby preventing hospital admission, improve quality of life, and reducing the burden of disease on healthcare services.[129] However, only appropriate technologies which succeed in engaging the patient can instigate this positive change. This engagement depends on the design and suitability of the technology to this complex elderly cohort, and many technology designs that fall short of this are discarded by their user-base, if they fail to meet their needs. The same can be said for the healthcare staff treating heart failure, who have similar needs, and require a certain level of engagement, before they are willing to disrupt their current practice in order to implement a new remote care device.[130]

This systematic review aims to explore these new remote distance technologies in chronic heart failure. In particular, it examines the effect these technologies have on patient's engagement with their care, and is coupled with an evaluation of the healthcare providers' needs. There were two main areas of interest: (a) the factors which determine the patients' decision to adopt, engage and continue to use the remote care intervention; and (b) the factors which contribute to the level of engagement of clinical and non-clinical staff in the implementation of a specific remote care intervention. Further information on remote care technology, along with supporting justification for this study and the methods used, can be found in the study protocol in Appendix 2.

2.1.1 Current perspectives on engagement with technology in heart failure

Previous reviews on technology adoption have highlighted the widespread prevalence of non-engagement with healthcare technologies, and have derived their own theories to help predict and mitigate this issue. A meta-ethnography by Greenhaigh and colleagues[131] looking into technology-supported health programs generated the

NASSS framework which identifies 7 critical domains that impact whether a technology is adopted. These are summarised under the headings of: the condition; the technology; the value proposition; the staff involved; the organisation; the social/institutional context, and finally the interaction between all these domains combined. While this approach goes some way to explaining mechanisms of non-adoption, it is a complex framework that does not lend itself to be applied to specific heart failure remote care technologies. Its scope is wide enough to give insights into the dynamic between users and medical technologies but it does not focus on specific conditions or interventions based around a single user base.

In contrast, this review will focus specifically on the heart failure patient cohort and create combine perspectives of the patient, carer and healthcare staff as separate user groups interacting with the same technology in different ways. In this way it narrows down the domains of 'the staff involved' or the 'adopter system' and treats it as a separate entity the 'user'. By focusing on a single condition of heart failure we aim to identify the unique contexts and issues found in this cohort to fully personalise engagement models around this vulnerable patient group.

To highlight this issue, Greenhaigh and colleagues[132] were also involved in studying the issues of poor uptake of heart failure technologies in clinical trials. They identified potential barriers to technology interaction and the 'tension' involved between expected management of the staff and practical realities of patients living with a chronic condition, who are likely to be isolated and vulnerable. They also constructed the paradigms of 'warm' personal face-to-face care versus 'cold' guideline-based biomarker/observation-rich clinical care. These observations provide a useful indication of the types of dynamics involved during trials of technology in heart failure patients, from a top-down perspective. Thus it would be useful to consider how many

of these tensions become evident from examining patient and staff personal experiences in this review.

2.2 Objectives

This systematic review of the use of remote care health technologies to aid with the management of heart failure has the following six objectives:

i. To Identify, appraise and synthesise qualitative research evidence on factors identified as having an impact on patient engagement

ii. To identify, appraise and synthesise qualitative research evidence relating to engagement of healthcare staff

iii. To identify, appraise and synthesise potential health inequalities brought about by the introduction of novel technologies

iv. To identify hypotheses and schema from this synthesis for future consideration in the design, development, and implementation of novel remote care interventions to improve uptake and sustainability

v. To Identify hypotheses for consideration in the design of future clinical trials and feasibility studies of novel remote care interventions

vi. To identify and develop hypotheses for consideration in the distribution and application of future interventions in order to minimise the health inequality created by them

2.3 Methods

2.3.1 Search methods

The following databases were searched for relevant publications and studies published between 1/1/1990 – 5/6/2016:

- EMBASE
- Ovid MEDLINE (with in-process and other index publications)
- Pubmed
- Cochrane library
- Scopus

In addition, reference lists of all included studies were searched for relevant publications. Appendix 3 shows the full search criteria used for the EMBASE database.

2.3.2 Criteria for considering studies for this review

2.3.2.1 Types of included studies

Only primary studies which use qualitative methodologies to collect data (e.g. focus groups, interviews) or analyse data (e.g. thematic analysis, grounded theory) were included. To differentiate qualitative from quantitative surveys in the literature, we defined a qualitative study as one which involves the participant to enter free-text comments or answer an open question. Therefore, ethnographies or patient observation studies which involved interviews with the participants were included in this criteria. Only English studies were included in the final selection.

2.3.2.2 Types of Participants

Patients

Patients diagnosed with adult chronic heart failure of all severities of disease were included. We excluded studies based on patients with congenital causes of heart failure or cardiomyopathy and paediatric heart failure.

Carers

This includes family members, spouses, care workers or other types of support provided to patients with adult chronic heart failure on a regular basis carrying out non-clinical tasks for their well-being.

Healthcare staff

We included healthcare staff who were involved in providing healthcare services to heart failure patients (i.e. physicians, specialist heart failure nurses) and who are involved in the use of remote healthcare technology. Also included were other staff members involved in the delivery, assessment, implementation or interpretation of a remote care technology or programme within healthcare settings (i.e. administrative staff, information technology staff, engineers, managerial or supervisory staff).

2.3.2.3 Settings

We included studies of remote care programmes in primary, secondary and tertiary settings as well as in community care settings. We also included studies in both public and private healthcare facilities. Studies were not excluded based on the country they were conducted in.

2.3.2.4 Interventions

For the purpose of this review, remote care programme is defined as any intervention or potential intervention that is accessible from the patient's home or local community (such as a local pharmacy), and which provides the patient with education, assessment, investigation results or otherwise replaces a service which would normally be offered within a formal clinical setting.

Remote care interventions were included if they provided a novel way of delivering an existing service in a remote fashion which was not part of an already existing, established care pathway. Therefore, current established interventions for heart failure and associated co-morbidities were excluded. These included long term oxygen therapy (LTOT), cardiac rehabilitation, and any self-care or disease education given at the point of contact in a clinical setting.

Remote care interventions were included if they had the potential to be used with all heart failure patients without excluding certain groups. For this reason, our definition of remote care excluded interventions which affect, track, monitor or otherwise interact with implantable medical devices which are only used in a select group of heart failure patients and do not require engagement since they are embedded.

Examples of services which would be considered as remote care technology included telemonitoring services, remote consultations, mobile apps tracking health status, and patient-directed online education programs.

2.3.2.5 Inclusions and exclusions summary

Inclusion criteria:

- Primary qualitative studies;
- Examining experiences of remote care technology;
- In the context of adult chronic heart failure care;
- Involving either patients or healthcare workers

Exclusion criteria:

- Non-English studies
- Non-qualitative methods, including questionnaires where there are no free-text sections
- Qualitative syntheses or meta-analyses that had no primary research component
- Studies with no remote care technology
- Technology associated solely with pacemakers or other implantable devices
- Studies with no patients that have a diagnosis of heart failure
- Studies involving only patients who had congenital causes of heart failure, cardiomyopathy, or below the age of 18 at diagnosis

2.3.3 Data collection and analysis

2.3.3.1 Study selection

We merged the bibliographic details from each electronic database search into one database, and removed duplicates. The abstracts were then checked for eligibility with the inclusion criteria. This eligibility criteria were discussed and calibrated between two authors (AA and JD) prior to the initial screening. A random sample of 30% of

the abstracts were screened independently by the two reviewers. Disagreements were resolved by consensus between the two reviewers, following which, one of the reviewers (AA) continued to screen the remaining abstracts for eligibility using the double-screened sample as a foundation.

Full publication of studies identified in stage one were obtained and assessed by two reviewers (AA and JD). Any disagreements in the double checking stage were discussed until a consensus was reached. Included full texts had their references extracted and these were then screened against the same eligibility criteria and de-duplicated. The remaining texts were added to the full text inclusions to comprise the final list of included texts.

2.3.3.2 Study Characteristics

Study characteristics were extracted using the Enhancing Transparency in Reporting the Synthesis of Qualitative Research (ENTREQ) statement,[133] which outlines guidance on reporting of quality synthesis reviews. Where interviews or focus groups took place, the study characteristics were extracted with guidance from the Consolidated Criteria for Reporting Qualitative Research (COREQ),[134] which outlines key aspects of reliable qualitative study to be reported on. We also used the PROGRESS-Plus framework[135] to create a more comprehensive review guideline for identifying health inequalities and characterising populations.[136] Its categories comprise the following: Place of residence, Race, Occupation, Gender, Religion, Education, Social capital, Socio-economic status, Age, Disability, Sexual orientation and other vulnerable and socially excluded groups.

2.3.3.3 Quality Assessment

Quality assessment of these studies ensures that the findings extracted are reliable and that bias is minimised.[137] Methodology of included literature was assessed using the NICE Quality Appraisal Checklist for Qualitative Studies,[138] which is based on the Critical Appraisal Skills Programme (CASP) framework, comprising 10 categories designed to make an informed assessment of the design and limitations of qualitative methods.[139] The CASP model has been widely used in similar thematic synthesis.[140] Assessment was checked by two authors independently and then discussed to reach a consensus about the quality of each report. Based on this quality assessment, each included study will be ranked in terms of excellent (++), good (+), or poor (-) quality. These rankings served to inform the quality of each of the first order codes generated, by linking each code to the papers it was generated from (Appendix 7). This allows the reader to assess each code on its own merit based on the quality of studies that supplied it. Rather than excluding the poor quality studies, we opted for a more inclusive study design to better encompass the range of user experiences and reach a saturation point for first order codes.

2.3.3.4 Thematic synthesis methodology

The process of the review was guided by the thematic analysis model of qualitative evidence synthesis.[141]

Generating first order codes

The first part of the synthesis involved extracting the preliminary or 'first-order' codes which are specific samples of text from each study that demonstrate user experience pertaining to remote care. Due to the difficulty of differentiating between primary study findings, author interpretation, and key findings of included studies, an

unstructured approach was taken to the initial results data extraction. We treated all text found within the 'results' or 'findings' sections of included publications as extractable data, including those found within abstracts. This textual data was extracted verbatim using specialised software designed for qualitative data analysis (EPPI-Reviewer 4, Version 4.7.1.2). For each study, this process was conducted by a single reviewer and cross checked by a second.

We used line-by-line coding techniques, whereby each sentence was interpreted by the reviewer and categorised under a code (a short, descriptive title) that was related to a certain experience, and these became our first order codes. First order codes were generated inductively from reading through the extracted text, and each code was given a description related to the extracted texts for which it encapsulated. A full list of the first order codes generated, along with the associated detailed description of each can be found in Appendix 4.

Generating second order codes

The first order codes were then grouped together under more general titles – the second order codes, which were umbrella terms that bridged together commonalities between multiple first order codes. Rather than being descriptive based on the text of included studies, the grouping of second order codes was subjective by nature.

To generate these second order codes, the first order codes were first categorised into one of three population cohorts: patients, carers and healthcare staff. Within these sections they were separated into two segments, positive and negative experience codes. Then each main author (AA and JD) generated their own list of associations between codes and grouped them together subjectively. Then a patient advisory group

was invited to contribute to this stage of the interpretation. The advisory group was involved at the outset of this project. The group created their own groupings based on this first code list as a team. All three sets of groupings (from AA, JD and the patient advisors) were then compared and a final grouping list was decided on via iterative consensus between the main authors.

Generating core concepts

Once the second order codes were generated, the reviewers reflected on the content of the examined studies and began a process of third order concept creation based on patterns and inferences observed from the entirety of the review process. Third order concepts were guided by the review question itself: What factors of remote care technology affected the engagement of the users?

These 'core concepts' were tied to the aims of the review and finalised by consensus from the main authors. Due to the associative nature of concept generation, many of the concepts tend to tie together, in particular concepts between patients and carers appeared very similar, though the meaning of the concept differs slightly depending on the population. The development of core concepts is a qualitative approach borne from immersion in the text and continuous revision of the findings; it is therefore an *ad hoc* summary of the understanding gained by the reviewers and serves as a subjective reflection for the purpose of answering the review's objectives.

Synthesising the themes

Both the core concepts and second order codes were finally consolidated to create overarching umbrella terms known as themes, which were designed to be universal

across patients, healthcare staff and carers, and seek to encapsulate all aspects of experiential user engagement. In much the same way that second order codes summarise the first order codes, the general themes were created by examining all the second order codes and core concepts together to find commonalities between them, and link them together under umbrella terms. The stark difference being that rather than separating codes between the user groups of patients, healthcare staff and carers, the general themes would encompass codes from all 3 cohorts into a unified thematic framework. As a result, the themes are described in very general terms but are critical to the precept of engagement with remote care. The aid of the patient participation group was also vital in establishing meaningful nomenclature for each of the themes and what they encompass. At all stages of the review, the authors reflected on their own background and position and how it would affect the design, analysis and interpretation of the research conducted.[141] A summary of the first order codes and how they eventually aligned to create our overall themes can be found in Appendix 9.

2.4 Results

2.4.1 Studies Selected

Our initial search criteria found 4842 matching studies. 243 were duplicates and were excluded. The remaining studies were screened by two reviewers, and based on their title and abstract, 4366 were excluded because they did not meet the inclusion criteria. The full texts of the remaining 233 studies were reviewed, and a further 195 were excluded as they did not meet the inclusion criteria. The remaining 38 studies were included in the full review. We found an additional 5 studies from the references of our included studies. As a result, 43 studies were included in the final review (see Figure 2.1). All reasonable attempts were made to access the full texts of studies where

required, including searching via multiple institutional and NHS healthcare access portals, and requesting papers from academic library resources when the digital versions were not available. Despite these steps, we were unable to obtain 25 of the abstracts and 3 of the full texts during the selection process.

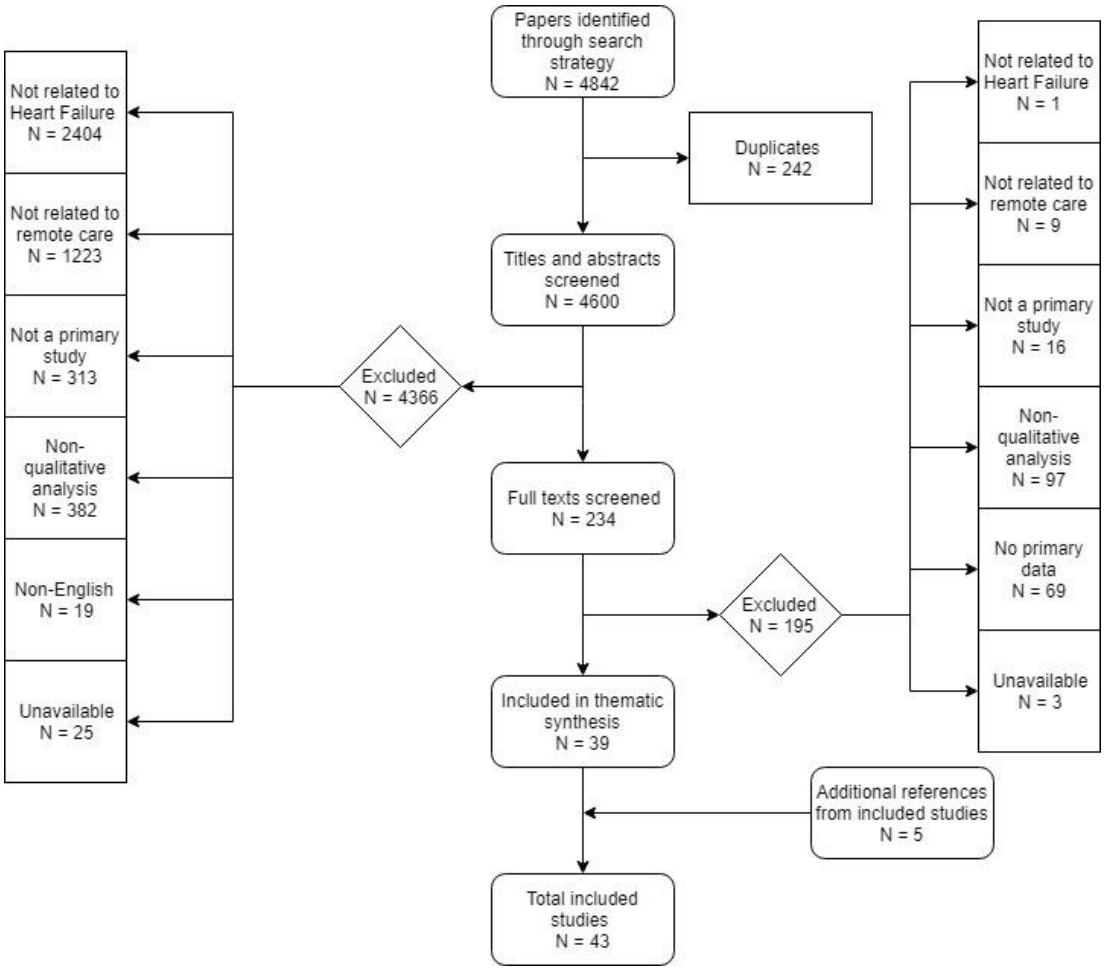

Figure 2.1 Flowchart of the sequence of exclusions for studies matching the search strategy, including reasons for exclusions

2.4.2 Overview of included studies

2.4.2.1 Intervention types

Out of the 43 included studies, various different types of remote care were employed, and thus the perspectives which feed into the final thematic analysis is reflective of these interventions. An overview of the included studies as well as the first order codes extracted are summarised in the main results (Table 2.1).

Remote monitoring systems and variants of this intervention were used in 28 studies. Remote monitoring tools involve teleconferencing or ways to monitor health measurements remotely to allow healthcare staff to review a patient's status from their home.[142-169] Clinical decision tools, which are usually automated systems that complement clinician management plans, were trialled in 4 studies.[147, 170-172] Patient health information platforms, where health information is accessible by the patient as needed, were included in 4 studies.[147, 173-175] Online management tools via an online portal, where a patient could obtain information for self-care or their medical management, were included in 3 studies.[147, 175, 176] Educational tools, a type of remote care designed around giving patient information for self-care through various means, were trialled in 3 studies.[147, 177, 178] Community remote care, involving occasional home visits by nurses, comprised 2 studies.[179, 180] There was only one instance each of the following interventions: telephone consultation,[181] peer-support system,[182] and pharmacy consultation.[183] One study delivered a concept of a remote care intervention and gathered opinions based on this theoretical design.[184]

2.4.2.2 Duration of intervention

In terms of duration of intervention, 16 studies had an unstated duration of intervention, [142, 147, 150, 153, 155, 161, 163, 165, 167-169, 172, 179, 180, 183, 184] 5 studies lasted just one day,[157, 170, 173, 176, 178], 1 study lasted between 2-7 days,[144] 2 studies lasted between 1-4 weeks,[154, 160] 8 studies lasted between 1-3 months,[143, 145, 148, 162, 164, 175, 177, 182] 4 studies lasted between 3-6 months,[146, 156, 158, 181] 4 studies lasted between 6-12 months,[149, 151, 159, 166] and 3 studies lasted over one year.[152, 171, 174]

2.4.2.3 Location of studies

A variety of countries were involved in the included studies where the intervention was trialled, most commonly the USA (n=15),[142, 147, 154, 160, 162-165, 173, 174, 176, 177, 181, 182, 184] followed by the UK (n=11),[143, 146, 150, 155, 156, 158, 159, 168, 169, 172, 183] Sweden (n=6),[148, 152, 153, 175, 178, 179] and Canada (n=6).[149, 166, 167, 170, 171, 180] One study each took place in Mexico,[142] Denmark,[144] Switzerland,[145] New Zealand,[151] and Australia.[157]

2.4.2.4 Demographics

A total of 8 studies included perspectives from healthcare staff alone,[155, 161, 163, 168-172] while 24 studies included patients alone.[142, 143, 145-148, 152-154, 157-159, 162, 164, 165, 173, 175-177, 179-182, 184] One study included only patients and their carers,[144] 8 studies included both patients and healthcare staff perspectives,[150, 156, 160, 166, 167, 174, 178, 183] and 2 studies included all three groups of healthcare staff, patients and carers.[149, 151]

Using the PROGRESS-Plus analysis criteria, further demographic information and inequalities data was obtained. The average age of participants in all studies was 68 years. In terms of missing data, 28 studies had no information on participant ethnicity.[142-150, 152, 153, 155, 156, 159-161, 163, 164, 166, 168-172, 175, 178, 179, 183] 11 studies had no information about gender. The number of female participants in all studies was less than half (47.8%) that of male participants where these numbers were explicitly stated. [143, 148, 150, 155-157, 161, 169-172] Only one study contained information regarding the religion of participants,[180] and only 9 studies reported on the socio-economic status of participants.[146, 151, 162, 167, 174, 182-184] The frequency of Caucasian/White ethnicity was greatest in all studies where it was recorded. The data extract of the patient characteristics data from the PROGRESS-Plus framework can be seen in Appendix 5.

2.4.2.5 Quality assessment

Using the NICE Quality Appraisal Checklist for qualitative studies, 12 studies were assessed as very high quality in that all or most of the checklist criteria had been fulfilled, and where they had not been fulfilled, the conclusions were very unlikely to alter as a result.[144, 146, 149, 151, 153, 157-159, 161, 166, 167, 174, 177, 184] 18 studies were assessed as moderate to high quality (some of the checklist criteria fulfilled, and where they had not been fulfilled, or not adequately described, the conclusions are unlikely to alter).[142, 143, 145, 152, 155, 165, 169-171, 175, 176, 179, 180, 182, 183] 13 studies were assessed as poor quality, wherein few or no checklist criteria had been fulfilled and the conclusions were likely or very likely to alter.[147, 148, 150, 154, 156, 160, 162-164, 168, 172, 173, 178] Results of the NICE Quality Appraisal Checklist for each included study can be found in Appendix 6.

Table 2.1 Characteristics of studies included with the first order codes generated from each study

Study	Intervention	Methods and sampling	Codes generated
Abidi 2013: Usability Evaluation of Family Physicians' Interaction with the Comorbidity Ontological Modeling and ExecuTion System (COMET) Aim: Assessing usability of intervention with family physicians Country: Canada Funding: Green Shield Canada Foundation	Name: Comorbidity Ontological Modeling and ExecuTion System (COMET) Type: Clinical Decision Tool Setting: Physician workplace Duration: 1 day Details: 15-minute training session involving clinical scenarios to simulate patients with various HF issues and diagnostic problems.	Sample: 10 physicians Sampling: Purposive Data: Observation, questionnaires, 'Think aloud' sessions Analysis: Grounded theory Quality score: +	<u>Healthcare staff –ve experiences:</u> *"Inflexible guidance"* *"Lack of training"* *"Lack of education"* *"Not user friendly"*
Agrell 2000: Patients' Perceptions Regarding Home Telecare Aims: To elicit patients' perceptions regarding home telecare Countries: USA & Mexico Funding: Not reported	Name: American TeleCare Type: Remote monitoring (Telemonitoring) Setting: Patient's home Duration: Not stated Details: Telecare in patient's homes	Sample: 15 patients Sampling: Convenience Data: Interviews, questionnaires Analysis: Not stated Quality score: +	<u>Patient +ve experiences:</u> *"Patient-staff communication"* *"feels looked after"* <u>Patient -ve:</u> *"Lack of patient-staff communication"* *"Not user friendly"* *"Lack of privacy/ security"*
Barron 2013: Feasibility of providing personalized health information to older adults and their caregivers	Name: Johns Hopkins Patient Portal Type: Patient health information platform Setting: Clinic	Sample: 23 patients Sampling: Convenience	<u>Patient +ve experiences:</u> *"User friendly"* <u>Patient –ve experiences:</u> *"Not user friendly"*

Study	Intervention	Methods and sampling	Codes generated
	Duration: 1 day	Data: Interviews, questionnaires	*"Lack of training"* *"Lack of education"*
Aim: Assess feasibility of intervention	Details: Internet-based patient portal to help family caregivers to partner more effectively with the health care team.	Analysis: Not stated Quality score: -	<u>Carer +ve experiences:</u> *"Extra support"* *"Informative/ Educational"* *"User friendly"*
Country: USA Funding: Not reported			<u>Carer –ve experiences:</u> *"Lack of education"* *"Not user friendly"*
Bartlett 2014: The SMART personalised self-management system for congestive heart failure: results of a realist evaluation Aims: A realist evaluation of the intervention Country: UK Funding: Engineering and Physical Sciences Research Council	Name: SMART Personalised Self-Management System (PSMS) for heart failure Type: Remote monitoring (Telemonitoring) and self-monitoring Setting: Patient's home Duration: 1-3 months Details: A touch screen computer and a touch screen mobile device, as well as sensor devices to measure weight and blood pressure were provided. Together, the components of the system encouraged goal setting, enabled self-monitoring of symptoms and behaviour, encouraged the ongoing review of progress towards goals and provided access to quality-assured information about the condition.	Sample: 7 patients Sampling: Not stated Data: Interviews Analysis: Realist evaluation Quality score: +	<u>Patient +ve experiences:</u> *"Feels looked after"* *"Clinical knowledge"* *"Confidence/ motivation in self-care"* *"Involvement in self-care"* *"Confidence in management decisions"* *"Improvement from usual care"* *"User friendly"* *"New technology"* <u>Patient –ve experiences:</u> *"Lack of feedback"* *"No effect on self-care"* *"Lack of improvement"* *"Technical difficulties"* *"Lack of portability"* *"Technology overwhelming"* *"Irrelevant training"* *"Intrusive"* *"Cost"* *"Lack of options"* *"Extra work = tiring"*

Study	Intervention	Methods and sampling	Codes generated
Bekelman 2014: Feasibility and Acceptability of a Collaborative Care Intervention To Improve Symptoms and Quality of Life in Chronic Heart Failure: Mixed Methods Pilot Trial Aim: To determine the feasibility and acceptability of the intervention and identify necessary improvements Country: USA Funding: Department of Veterans Affairs	Name: The CASA (Collaborative Care to Alleviate Symptoms and Adjust to Illness) Type: Telephone consultations Setting: Patient's home Duration: 3-6 months Details: 3 step intervention: 1) nurse phone visits involving structured symptom assessments to alleviate breathlessness, fatigue, pain, or depression; 2) structured phone counselling targeting adjustment to illness and depression; 3) weekly team meetings with a palliative care specialist, cardiologist, and primary care physician focused on medical recommendations to primary care providers to improve symptoms.	Sample: 17 patients Sampling: Not stated Data: Interviews Analysis: Not stated Quality score: +	<u>Patient +ve experiences:</u> *"Psychosocial support"* *"Patient-staff communication"* *"Feels looked after"* *"Clinical knowledge"* *"Confidence/ motivation in self-care"* *"Involvement in self-care"* *"User friendly"* <u>Patient –ve experiences:</u> *"Reliance on staff"* *"Lack of patient-staff communication"* *"Lack of improvement"* *"Not user friendly"* *"Lack of education"* *"Irrelevant training"* *"Lack of options"*
Dinesen 2008: Under surveillance, yet looked after: Telehomecare as viewed by patients and their spouse/partners Aim: To understand the experiences and attitudes of patients and their spouses/partners with regard to the application of telehomecare technology within home hospitalisation	Name: 'Home hospitalisation' Type: Remote monitoring (Telemonitoring) Setting: Patient's home Duration: up to 1 week Details: District nurse visits twice daily - morning and evening and phone hospital nurses to exchange information and jobs. DN collects data: BP, pulse, weight, INR, ECG and sends wirelessly to hospital. Information is used for twice daily ward round. Patient discharged when stable.	Sample: 8 patients, 6 spouses Sampling: Purposive Data: Interviews Analysis: Thematic analysis Quality score: ++	<u>Patient +ve experiences:</u> *"Patient-patient communication"* *"Patient-staff communication"* *"Feels looked after"* *"Clinical knowledge"* *"Confidence/ motivation in self-care"* *"Involvement in self-care"* *"Confidence in management decisions"* *"Improvement from usual care"* *"New technology"* *"Flexible"* *"Comfort/ freedom at home"* <u>Patient –ve experiences:</u> *"Technical difficulties"*

Study	Intervention	Methods and sampling	Codes generated
Country: Denmark Funding: Spar Nord Fonden, Det Obelske Familiefond, Jyske Bank and Aalborg University			*"Adds extra concern for carers"* <u>Carer +ve experiences:</u> *"Feel patient is looked after"* *"Extra support"* <u>Carer –ve experiences:</u> *"Extra responsibility"* *"Change is stressful"* *"Causes concern for patient"* *"Control taken away"* *"Invasion of privacy"* *"Lack of education"* *"Lack of improvement"* *"Technical difficulties = stressful"*
Dubois 2001: Evaluation of patients' satisfaction with hospital-at-home care Aim: To measure patients' satisfaction with the intervention Country: Switzerland Funding: Public Health Department of the Canton of Vaud	Name: The H-Hcare Program Type: Remote monitoring (Telemonitoring) and Home visits Setting: Patient's home Duration: 1-3 months Details: A home-care program consisting of regularly scheduled nurse visits for medical patients already in hospital to be discharged home with rather than staying in hospital.	Sample: 107 patients Sampling: Not stated Data: Interviews, questionnaires Analysis: Thematic analysis Quality score: +	<u>Patient +ve:</u> *"Psychosocial support"* *"Feels looked after"* *"Confidence in management decisions"* *"Saves travel time"* *"Flexible"* *"Comfort/ Freedom at home"* <u>Patient –ve experiences:</u> *"Lack of patient-staff communication"* *"Responsibility = anxiety"* *"Unpredictable clinical management"* *"Lack of improvement"* *"Technical difficulties"* *"Lack of training"* *"Cost"* *"Lack of privacy/ security"* *"Lack of options"* *"Adds extra concern for carers"*

Study	Intervention	Methods and sampling	Codes generated
			"Lack of support for care" *"Extra work = tiring"* *"Uncomfortable at home"* *"Lack of efficiency/ co-ordination"* *"Cannot replace hospital care"* <u>Carer +ve experiences:</u> *"Feel patient is looked after"* <u>Carer –ve experiences:</u> *"Extra responsibility"* *"Change is stressful"*
Earnest 2004: Use of a Patient-Accessible Electronic Medical Record in a Practice for Congestive Heart Failure: Patient and Physician Experiences Aim: To evaluate the experiences of patients and physicians in a clinical trial of the intervention Country: USA Funding: Commonwealth Fund	Name: SPPARO, System Providing Patients Access to Records Online Type: Patient health information platform Setting: Patients' home and clinic Duration: 1-2 years Details: Patient-accessible electronic medical record that provides access to clinical notes, test results, health information, and a method of sending and receiving electronic messages to and from the clinic staff.	Sample: 16 patients, 7 physicians Sampling: Not stated Data collection: Focus-groups, interviews Analysis: Grounded theory Quality score: ++	<u>Patient +ve experiences:</u> *"Patient-staff communication"* *"Feels looked after"* *"Clinical knowledge"* *"Follow up/ co-ordination of care"* *"Confidence/ motivation in self-care"* *"Involvement in self- care"* *"Confidence in management decisions"* *"Popular"* <u>Patient –ve experiences:</u> *"Lack of patient-staff communication"* *"Medical jargon"* *"Not user friendly"* *"Lack of training"* *"Lack of education* *"Lack of privacy/ security"* <u>Healthcare staff +ve experiences:</u> *"Familiarity/ communication with patient"* *"Reduces error"* *"Important"* *"Encourages patient self-care"*

Study	Intervention	Methods and sampling	Codes generated
			"Increases patient knowledge" *"No change in workload"* <u>Healthcare staff –ve experiences:</u> *"Increases patient concern/ confusion"* *"Lack of patient-staff communication"* *"No improvement"* *"Increases errors"* *"Cost"* *"Health inequality"*
Fairbrother 2014: Telemonitoring for chronic heart failure: the views of patients and healthcare professionals – a qualitative study Aim: To understand the views of patients and professionals on the acceptability and perceived usefulness of telemonitoring in the management of chronic heart failure. Country: Scotland Funding: Scottish Centre for Telehealth and Telecare	Name: Intel Health Guide (IHG) Type: Remote monitoring (Telemonitoring) Setting: Patient's home Duration: 3-6 months Details: Touch-screen device allowing a daily self-assessment of symptoms using an online questionnaire. The device was connected to sensors that measured pulse rate, oxygen saturation, blood pressure, and weight daily. The IHG also contained educational content (in the form of online video-based content) to support patient self-management.	Sample: 18 patients Sampling: Purposive Data: Interviews Analysis: Framework analysis Quality score: ++	<u>Patient +ve experiences:</u> *"Patient-staff communication"* *"Feels looked after"* *"Clinical knowledge"* *"Confidence/ motivation in self-care"* *"Involvement in self-care"* *"User friendly"* *"Popular"* <u>Patient –ve experiences:</u> *"Reliance on staff"* *"Lack of patient-staff communication"* *"Responsibility = anxiety"* *"Unpredictable clinical management"* *"No effect on self-care"* *"Lack of improvement"* *"Technical difficulties"* *"Intrusive"* *"Cost"* <u>Healthcare staff +ve experiences:</u> *"Familiarity/ communication with patient"* *"Better knowledge of patient status"* *"Pro-active management"*

Study	Intervention	Methods and sampling	Codes generated
			"Confidence in management" <u>Healthcare staff –ve experiences:</u> *"Perceived dependence on staff"* *"Lack of patient-staff communication"* *"Not linked to records"* *"Inflexible guidance"* *"Not user friendly"* *"Lack of education"* *"No change in patient self-care"* *"No improvement"* *"Increased workload"* *"Patient selection decisions"* *"Cost"*
Finkelstein 2011: Implementing Home Telemanagement of Congestive Heart Failure Using Xbox Gaming Platform Aim: to explore whether it is possible to take advantage of the simplicity, popularity, and low cost of the Xbox360 to build a platform able to deliver a comprehensive disease management program within patients' homes Country: USA Funding: Not stated	Name: Home Automated Telemanagement (HAT) system Type: self-monitoring, remote monitoring (telemonitoring), clinical decision tool, patient health information platform, online management, educational tool Setting: Patient's home Duration: Not stated Details: The HAT system consists of home unit, HAT server and clinician unit. The home unit uses an Xbox 360 gaming platform and the Xbox360 controller for input. It allows a patient to record symptoms and weight and gives feedback about their condition over time. The physician can access the CHF HAT website to review patient data, track progress,	Sample: 10 patients Sampling: Not stated Data: Interviews Analysis: Not stated Quality score: -	<u>Patient +ve experiences:</u> *"Feels looked after"* *"Clinical knowledge"* *"Confidence/ motivation in self-care"* *"User friendly"* *"Popular"* *"Flexible"* <u>Patient –ve experiences:</u> *"Not user friendly"*

Study	Intervention	Methods and sampling	Codes generated
	make changes to medications, and set alerts. The HAT server then uses clinical decision support algorithms which alert the physician if any ominous trend is detected.		
Green 2006: Information system support as a critical success factor for chronic disease management: Necessary but not sufficient Aim: To identify critical success factors enabling clinical knowledge about effective and efficient chronic care management to be translated into primary care practice Country: Canada Funding: Canadian Institute for Health Research	Name: Chronic disease management (CDM) collaborative Type: Clinical decision tool Setting: Clinic Duration: 3-5 years Details: A web-based patient registry system with guideline-based flow sheet that allowed physicians to identify the patients in their practice with target chronic diseases and to monitor their care against a standard.	Sample: 30 physicians Sampling: Not stated Data: Interviews Analysis: Critical success factor analysis Quality score: +	<u>Healthcare +ve experiences:</u> *"Encourages teamwork"* *"Better knowledge of patient status"* *"Confidence in management"* *"Identifies priorities in care"* *"Reduces error"* *"Staff education"* *"User friendly"* *"Technical support"* *"Security/ privacy"* *"No change in workload"* *"Incentivisation"*
Gund 2008: Design Evaluation of a Home-Based Telecare System for Chronic Heart Failure Patients Aim: Evaluation of the usability of the intervention with heart failure patients. Country: Sweden	Name: Care@Distance Type: Remote monitoring (Telemonitoring), and self-monitoring Setting: Patient's home Duration: 1-3 months Details: Three component telecare system consisting of a home based patient terminal, an internet networked database, and a web	Sample: 2 patients Sampling: convenience Data: Interviews Analysis: Not stated Quality score: -	<u>Patient +ve experiences:</u> *"Patient-staff communication"* *"Feels looked after"* *"User friendly"* *"Popular"* *"Saves travel time"* *"Flexible"* <u>Patient –ve experiences:</u> *"Technical difficulties"* *"Not user friendly"*

Study	Intervention	Methods and sampling	Codes generated
Funding: VINNOVA	portal for the care providers. The home terminal is a tablet PC that will record blood pressure, weight, and symptoms via a blood pressure monitor and scale. Data from the patient terminal is accessed by the health care providers through the web portal, which is also used for managing the home terminal.		*"Intrusive"* *"Lack of options"* <u>Healthcare staff –ve experiences:</u> *"Not user friendly"* *"Lack of options"*
Hall 2014: Heart Failure Patients' Perceptions and Use of Technology to Manage Disease Symptoms Aim: This study explores patients' perceptions and current use of technology for managing HF symptoms Country: USA Funding: Finger Fellowship in Sustainable Health	Name: Blue Scale (Blue Box, Inc., Houston, TX) Type: Remote monitoring (Telemonitoring) Setting: Patient's home Duration: Not stated Details: The Blue Scale device tracks multiple vital sign readings important for HF patient home monitoring while the patient grasps handles that are large and attached to a reinforced base for adequate support and fall prevention.	Sample: 15 patients Sampling: Not stated Data: Interviews Analysis: Constant comparison Quality score: +	<u>Patient +ve experiences:</u> *"Patient-staff communication"* *"Feels looked after"* *"Clinical knowledge"* *"Confidence/ motivation in self-care"* *"Improvement from usual care"* *"New technology"* *"Saves travel time"* *"Comfort/ freedom at home"* <u>Patient –ve experiences:</u> *"Reliance on staff"* *"Technical difficulties"* *"Medical jargon"* *"Technology overwhelming"* *"Lack of education"* *"Unreliable information"* *"Cost"* *"Lack of privacy/ security"* *"Extra work = tiring"*
Heisler 2007: "I Am Not Alone": The Feasibility and Acceptability of Interactive Voice Response–Facilitated Telephone Peer Support	Name: Interactive voice-response based platform Type: Peer-support system Setting: Patient's home	Sample: 20 patients Sampling: Convenience Data: Interviews, questionnaires	<u>Patient +ve experiences:</u> *"Psychosocial support"* *"Patient-patient communication"* *"Confidence/ motivation in self-care"* <u>Patient –ve experiences:</u>

Study	Intervention	Methods and sampling	Codes generated
Among Older Adults With Heart Failure Aim: Evaluating the feasibility and acceptability of the intervention to facilitate telephone peer support among older adults with heart failure Country: USA Funding: Not stated	Duration: 1-3 months Details: Peer support in conjunction with a structured program of education and assistance. Participants were asked to contact their partner at least once a week using the toll-free IVR calling line.	Analysis: Not stated Quality score: +	*"Lack of patient-patient communication"* *"Lack of patient-staff communication"* *"No effect on self-care"* *"Lack of improvement"* *"Lack of training"*
Hunting 2015: A multi-level qualitative analysis of Telehomecare in Ontario: challenges and opportunities Aim: To explore the factors which facilitate or impede the implementation of the program Country: Canada Funding: Ontario Ministry of Health and Long Term Care (MOHLTC)	Name: Ontario Telemedicine Network (OTN) Type: Remote monitoring (Telemonitoring) Setting: Patient's home Duration: 6 months Details: The program involves: i) telehomecare nurses with whom patients can interact by telephone; ii) daily transmission of patient data (weight, blood pressure, oxygen levels, and answers to daily questionnaire) to a nurse via a remote monitoring device; iii) individualized care based on patient needs (e.g., following up with patient if their data is outside of a normal range and weekly coaching sessions); and iv) communication regarding patient health concerns between the nurse and other members of the patient's circle of care.	Sample: 39 patients/ caregivers, 23 healthcare staff, 2 technicians, 12 administrators, 13 decision makers Sampling: Purposive Data: Interviews, ethnographic observation Analysis: Grounded theory thematic analysis Quality score: ++	<u>Patient +ve experiences:</u> *"User friendly"* *"Confidence/ motivation in self-care"* *"Feels looked after"* *"Saves travel time"* *"Patient-staff communication"* *"Follow up/ co-ordination of care"* <u>Patient –ve experiences:</u> *"Not user friendly"* *"Language barriers"* *"Reliance on staff"* *"Intrusive"* *"Lack of portability"* *"No effect on self-care"* *"Irrelevant training"* <u>Carer +ve experiences:</u> *"Feels patient is looked after"* <u>Healthcare staff +ve experiences:</u> *"Encourages patient self-care"* *"Saves travel time"*

Study	Intervention	Methods and sampling	Codes generated
			"Technical support" *"Encourages teamwork"* *"Better knowledge of patient status"* *"Automated saves time"* *"Important"* *"Local champions"* *"Improvement from usual care"* <u>Healthcare staff –ve experiences:</u> *"Increased workload"* *"Perceived dependence on staff"* *"Not linked to records"* *"Lack of staff-staff communication"* *"Lack of patient-staff communication"* *"Patient selection decisions"* *"Health inequality"* *"Slow to change practice"* *"Cost"*
Johnston 2010: Automated weight monitoring in chronic heart failure: the excluded majority Aim: To Investigate how the intervention might affect the care of the patients in a wider sense than solely the cost-effectiveness Country: UK Funding: Not stated	Name: Remote automated weight monitoring system Type: Remote monitoring (Telemonitoring) Setting: Patient's home Duration: Not stated Details: Not stated	Sample: 14 patients, 10 carers, 4 nurses Sampling: Not stated Data: Focus groups, interviews Analysis: Thematic analysis Quality score: -	<u>Patient +ve experiences:</u> *"Psychosocial support"* *"Feels looked after"* *"Confidence/ motivation in self-care"* <u>Patient –ve experiences:</u> *"Lack of patient-staff communication"* *"Lack of feedback"* *"Lack of improvement"* *"Technical difficulties"* *"Not user friendly"* *"Lack of education"* *"Intrusive"* *"Cost"* <u>Carer +ve experiences:</u>

Study	Intervention	Methods and sampling	Codes generated
			"Feels patient is looked after"
Kenealy 2015: Telecare for Diabetes, CHF or COPD: Effect on Quality of Life, Hospital Use and Costs. A Randomised Controlled Trial and Qualitative Evaluation Aim: To assess the effect of telecare on health related quality of life, self-care, hospital use, costs and the experiences of patients, informal carers and health care professionals Country: New Zealand Funding: Primary Health Care Strategic Innovations Fund	Name: 'Health Hub ' supplied by Docobo Type: Remote monitoring (Telemonitoring) and self-monitoring Setting: Patient's home Duration: 6-12 months Details: The hub was a small device with a LCD display to provide instructions, ask disease-specific questions, or convey short messages from the nurses monitoring the data. Patients were also provided with electronic weighing scales, a blood pressure monitor, a pulse oximeter and a glucometer for diabetics. Patients enter data manually into the hub which is then relayed to the monitoring stations where they were viewed by the nurses.	Sample: 47, combined patients, carers and healthcare professionals Sampling: Purposive Data: Focus groups, interviews Analysis: Thematic analysis Quality score: ++	<u>Patient +ve experiences:</u> *"Psychosocial support"* *"Patient-staff communication"* *"Feels looked after"* *"Clinical knowledge"* *"Confidence/ motivation in self-care"* *"Involvement of self-care"* *"Confidence in management decisions"* *"Improvement from usual care"* *"New technology"* *"Popular"* *"Saves travel time"* *"Flexible"* <u>Patient –ve experiences:</u> *"Technical difficulties"* *"Lack of portability"* *"Extra work = tiring"* <u>Carer +ve experiences:</u> *"Feels patient is looked after"* *"Informative/ educational"* <u>Healthcare staff +ve experiences:</u> *"Familiarity/ communication with patient"* *"Important"* *"Encourages patient self-care"* *"Increases patient knowledge"* *"No change in workload"* <u>Healthcare staff –ve experiences:</u> *"Technical difficulties"* *"Increased workload"* *"Increases errors"*

Study	Intervention	Methods and sampling	Codes generated
Leslie 2006: Clinical decision support software for management of chronic heart failure: Development and evaluation Aim: To develop and evaluate clinical decision support software (CDSS) to aid physicians treat patients with chronic heart failure (CHF) Country: UK Funding: Not stated	Name: Clinical decision support software (CDSS) Type: Clinical decision tool Setting: Clinic and hospital Duration: Not stated Details: The evidence base used to generate the clinical information within the tool was derived from published guidelines and papers. This information was used to create a series of 'yes/no' flow diagrams for diagnosis, initiation and up-titration of drug treatments. Various combinations of these 'inputs' produced a range of 'outputs' designed as short phrases containing clinical advice to allow users to check their suspicions against a pattern of clinical features which have been shown to exclude or include a diagnosis of heart failure, e.g. a normal electrocardiogram, history of previous myocardial infarction etc.	Sample: 5 healthcare staff Sampling: Not stated Data: Interview Analysis: Not stated Quality score: -	<u>Healthcare staff +ve experiences:</u> *"Confidence in management"* *"Identifies priorities in care"* *"Improvement from usual care"* *"Important"* *"Increases patient knowledge"* *"Staff education"* *"User friendly"* *"Technical support"* *"Automated saves time"* <u>Healthcare staff –ve experiences:</u> *"Inflexible guidance"* *"Not user friendly"* *"Computer literacy"* *"Lack of equipment/ support"* *"Lack of education"* *"Increased workload"* *"Slow to change practice"* *"Lack of options"*
Lind 2014: Telehealth for "the Digital Illiterate" – Elderly Heart Failure Patients' Experiences Aim: The aim of this paper was to explore and describe the patients' and spouses' experiences in using the system	Name: Digital pen technology (www.anoto.com),The Health Diary system Type: Remote monitoring (Telemonitoring) and self-monitoring Setting: Patient's home Duration: 1-2 years Details: This comprises the pen and ordinary paper with a printed close-to-invisible pattern	Sample: 7 patients Sampling: Not stated Data: Interviews Analysis: Content analysis Quality score: +	<u>Patient +ve experiences:</u> *"Patient-staff communication"* *"Feels looked after"* *"Clinical knowledge"* *"Involvement in self-care"* *"Confidence in management decisions"* *"Improvement from usual care"* *"User friendly"* *"Saves travel time* <u>Patient –ve experiences:</u>

Study	Intervention	Methods and sampling	Codes generated
	read by a camera inside the digital pen. The pen is used as an ordinary ball-point pen, but the strokes made by the pen are recorded and transferred via mobile internet to a server. The Health Diary system supported daily reports on shortness of breath, intake of medications, weight and other measurements. The diary also allowed free text messages to the care provider. The system was monitored by health professionals and generated alarms if patient-reported values were below/above certain limits.		*"Lack of improvement"* *"Not user friendly"* *"Technology overwhelming"*
Lowrie 2014: Experiences of a community pharmacy service to support adherence and self-management in chronic heart failure Aim: We aimed to explore and portray in detail, the perspectives of patients receiving, and pharmacists delivering an enhanced, pay for performance community pharmacy HF service Country: UK Funding: Not stated	Name: Community pharmacy-based heart service Type: Pharmacy consultations Setting: Pharmacy Duration: Not stated Details: Training received by each participating community pharmacist comprised 3 h of contact time with experienced pharmacists and nurses, including mock consultations with patients. The community pharmacy was then expected to deliver the service to referred patients on a monthly or two–monthly basis. The content of each consultation included review of each medicine, monitoring of symptoms, identified care issues, adherence issues, weight monitoring, smoking status, and referral.	Sample: 65 patients, 10 pharmacists Sampling: Data: Focus groups, interviews Analysis: Framework analysis Quality score: +	<u>Patient +ve experiences:</u> *"Psychosocial support"* *"Patient-staff communication"* *"Feels looked after"* *"Clinical knowledge"* *"Confidence/ motivation in self-care"* *"Involvement in self-care"* *"Improvement from usual care"* *"Popular"* *"Saves travel time"* <u>Patient –ve experiences:</u> *"Lack of improvement"* *"Lack of education"* *"Lack of efficiency/ co-ordination"* <u>Healthcare staff +ve experiences:</u> *"Familiarity/ communication with patient"* *"Better knowledge of patient status"* *"Pro-active management"* *"Confidence in management"*

Study	Intervention	Methods and sampling	Codes generated
			"Important" *"Encourages patient self-care"* *"Increases patient knowledge"* *"User friendly"* <u>Healthcare staff –ve experiences:</u> *"Lack of patient-staff communication"* *"Lack of staff-staff communication"* *"Inflexible guidance"* *"Lack of training"* *"Lack of education"* *"No change in patient self-care"* *"Increased workload"*
Lundgren 2015: Internet-based cognitive behaviour therapy for patients with heart failure and depressive symptoms: A proof of concept study Aim: To evaluate the feasibility of the ICBT program in regard to depressive symptoms, the time used by health care providers to give feedback, and participants' perceptions of the ICBT program Country: Sweden Funding: Medical Research Council of Southeast Sweden	Name: Internet-based-CBT (ICBT) Type: Patient health information platform and online management Setting: Patient's home Duration: 1-3 months Details: The treatment program and feedback were delivered via an internet platform. The core of the program material was adapted to heart failure patients and included psycho-education, behaviour activation, and problem-solving over a nine-week program.	Sample: 7 patients Sampling: Not stated Data: Interviews Analysis: Content analysis Quality score: +	<u>Patient +ve experiences:</u> *"Clinical knowledge"* *"Confidence/ motivation in self-care"* *"Flexible"* <u>Patient –ve experiences:</u> *"Technical difficulties"* *"Extra work = tiring"*

Study	Intervention	Methods and sampling	Codes generated
Lyngå 2013: Perceptions of transmission of body weight and telemonitoring in patients with heart failure? Aim: The aim of this study was to explore and describe patients perceptions of transmission of body weight (BW) and telemonitoring, regularly accomplished from patients homes to an HF clinic Country: Sweden Funding: Not funded	Name: Wireless electronic scale Type: Remote monitoring (Telemonitoring) and self-monitoring Setting: Patient's home Duration: Not stated Details: Patients in the intervention group were given an electronic scale to place in their home and asked to weigh themselves daily. The weight measurements were automatically trans- mitted to a heart failure clinic. If a weight gain was detected of 2 kg in 3 days, the patients were contacted by telephone. If there were signs of deterioration in the patients (e.g., increased breathlessness or tired- ness, swollen legs or difficulties to lay flat in bed, together with increased BW), the dose of diuretics was temporally increased.	Sample: 20 patients Sampling: Purposive Data: Interviews Analysis: Phenomenology Quality score: ++	<u>Patient +ve experiences:</u> *"Patient-staff communication"* *"Feels looked after"* *"Clinical knowledge"* *"Confidence/ motivation in self-care"* *"Involvement in self-care"* *"Confidence in management decisions"* *"User friendly"* *"New technology"* <u>Patient –ve experiences:</u> *"Lack of patient-staff communication"* *"Responsibility = anxiety"* *"Lack of feedback"* *"No effect on self-care"* *"Technical difficulties"*
Nanevicz 2000: The feasibility of a telecommunications service in support of outpatient congestive heart failure care in a diverse patient population Aim: We report on the feasibility and efficacy of using a home telemonitoring service as an adjunct to the outpatient care of heart failure	Name: Telemonitoring service provided by Alere Medical Inc., San Francis- co, CA Type: Remote monitoring (Telemonitoring) Setting: Patient's home Duration: 1-4 weeks Details: The system combines a scale with a simple display monitor. The patient stood on the scale activating the monitor's pre-recorded voice which told the patient his or her weight and how it compared to his or her	Sample: 50 patients Sampling: Purposive Data: Questionnaires Analysis: Not stated Quality score: -	<u>Patient +ve experiences:</u> *"Clinical knowledge"* *"Popular"* <u>Patient –ve experiences:</u> *"Technical difficulties"* <u>Healthcare staff –ve experiences:</u> *"Increased workload"*

Study	Intervention	Methods and sampling	Codes generated
patients from diverse backgrounds Country: USA Funding: American Heart Association	ideal weight. The monitor then asked the patient a number of heart failure symptomatology questions (as defined by the physician), to which the patient responded by pressing 'yes' or 'no' on the monitor. Weight and symptom information was then transmitted over the telephone line to a nurse who contacted the patient if there was a weight gain of 5 lbs or a weight loss of 10 lbs within 5 days, or reported symptoms for 3 consecutive days. The nurse then notified the physician of any patient alerts or information. In addition, patients received weekly or biweekly calls from the nurse to review symptoms and medications, and to discuss an educational topic relevant to the patient's medical history. The educational modules covered general information about heart failure, diet, medications, symptom recognition, exercise, and lifestyle.		
Nässtrom 2015: Heart failure patients' descriptions of participation in structured home care Aim: To examine how heart failure patients receiving structured home care described participation in the care	Name: Structured home care – The Heart Failure at Home Model Type: Home visits Setting: Patient's home Duration: Not stated Details: The patients received care that involved a multidisciplinary team with physicians and nurses, optimized treatment according to guidelines, educational strategies	Sample: 19 patients Sampling: Purposive Data: Interviews Analysis: Content analysis Quality score: +	<u>Patient +ve experiences:</u> *"Patient-patient communication"* *"Patient-staff communication"* *"Feels looked after"* *"Clinical knowledge"* *"Confidence/ motivation in self-care"* *"Involvement in self-care"* *"Confidence in management decisions"* *"Improvement from usual care"* <u>Patient –ve experiences:</u> *"Reliance on staff"*

Study	Intervention	Methods and sampling	Codes generated
Country: Sweden Funding: Swedish Heart and Lung Association	for patients/families/caregivers, and increased accessibility to care. The patients could contact the home care team at all hours		*"Lack of options"*
Odeh 2014: Implementing a telehealth service: nurses' perceptions and experiences Aim: To elicit practice nurses' perceptions of the telehealth service Country: UK Funding: Not stated	Name: A remote patient monitoring (RPM) telehealth service Type: Remote monitoring (Telemonitoring) Setting: Workplace Duration: Not stated Details: The system consisted of a set of peripheral devices at the patient's home, including blood-pressure monitor, pulse oximeter, thermometer, weighing scales and peak-flow monitor/spirometer. According to preapproved set plans, the patient takes the measurements and answers a series of questions about symptoms. The readings are transmitted to a monitoring centre where they are triaged. If the data fall outside the parameters set for the patient, a trigger will be generated and forwarded to the practice nurse. The nurse can also access the data remotely, enabling monitoring trends over time and making informed decisions accordingly.	Sample: 7 nurses Sampling: Not stated Data: Email interviews Analysis: Thematic analysis Quality score: +	<u>Healthcare staff +ve experiences:</u> *"Familiarity/ communication with patient"* *"Encourages patient self-care"* <u>Healthcare staff –ve experiences:</u> *"Lack of staff-staff communication"* *"Not linked to records"* *"Technical difficulties"* *"Lack of equipment/ support"* *"Lack of training"* *"Increased workload"* *"Slow to change practice"* *"Lack of options"* *"Patient selection decisions"* *"Cost"* *"Lack of evidence of effectiveness"*
Paget 2010: Using home telehealth to empower patients to monitor and manage long term conditions	Name: Genesis home monitor Type: Remote monitoring (Telemonitoring) Setting: Patient's home Duration: 12 weeks	Sample: 22 patients, nurses (unknown number) Sampling: Not stated Data: Questionnaires	<u>Patient +ve experiences:</u> *"Feels looked after"* *"Confidence/ motivation in self-care"* *"Involvement in self-care"* *"Comfort/ freedom at home"* *"Clinical knowledge"*

Study	Intervention	Methods and sampling	Codes generated
Aim: Evaluation of the intervention Country: Wales Funding: Welsh assembly government grant	Details: The genesis monitor is a home device with a blood pressure cuff and pulse oximeter attached, and is also connected to a weighing scales. The monitor activates at a pre-set time daily and instructs the patient to take their measurements and answer yes/no questions about their symptoms set by a nurse. The patient can request a visit by the nurse from the monitor. The information is sent to a nurse via a telephone line, and the reports can be printed by the patient.	Analysis: Not stated Quality score: -	*"User friendly"* <u>Patient –ve experiences:</u> *"Technical difficulties"* *"Lack of support for care"* <u>Healthcare staff +ve experiences:</u> *"User friendly"* <u>Healthcare staff –ve experiences:</u> *"Technical difficulties"* *"Increases patient concern/ confusion"* *"Lack of equipment/ support"* *"Increases errors"* *"Lack of training"* *"Slow to change practice"* *"Increased workload* *"Patient selection decisions"*
Payne 2015: Usability Testing of an Internet-Based e-Counselling Platform for Adults With Chronic Heart Failure Aim: A prototype website evaluation to promote self-care in patients with heart failure via a counselling platform Country: USA Funding: Canadian Institutes of Health Research	Name: CHF-CePPORT - Canadian e-Platform to Promote Behavioural Self-Management in Chronic Heart Failure Type: Online management Setting: Clinic Duration: 1 day Details: 28 e-sessions delivered over a 12 month period consisting of a self-help video, educational content, interactive e-tools, and e-trackers for behaviour change. In this study, the participants were exposed to draft content to help refine it, not exposed to the completed 12-month package.	Sample: 7 patients Sampling: Purposive Data: Interviews and questionnaires Analysis: Content analysis Quality score: +	<u>Patient +ve experiences:</u> *"Psychosocial support"* *"Feels looked after"* *"Clinical knowledge"* <u>Patient –ve experiences:</u> *"Not user friendly"*

Study	Intervention	Methods and sampling	Codes generated
Rahimpour 2008: Patients' perceptions of a home telecare system Aim: To identify any major factors that could affect patients' perceptions of the intervention and use the findings to contribute to development of a theoretical framework for patient acceptance Country: Australia Funding: Funded by company developing intervention	Name: Home Telecare Management System (HTMS) Type: Remote monitoring (Telemonitoring) Setting: Hospital Duration: 1 day Details: The participants were shown a videotape demonstrating the range of clinical measurements the HTMS could provide: blood pressure, spirometry, temperature, weight, heart rate, ECG and providing feedback to patients including medication reminders and measurement scheduling.	Sample: 77 patients Sampling: Purposive Data: Focus groups Analysis: Thematic analysis Quality score: ++	<u>Patient +ve experiences:</u> *"Psychosocial support"* *"Feels looked after"* *"Clinical knowledge"* *"Follow up/ co-ordination of care"* *"Confidence/ motivation in self-care"* *"Involvement in self-care"* *"Confidence in management decisions"* *"Improvement from usual care"* *"User friendly"* *"Popular"* *"Saves travel time"* *"Comfort/ freedom at home"* <u>Patient –ve experiences:</u> *"Lack of patient-staff communication"* *"Responsibility = anxiety"* *"Technical difficulties"* *"Not user friendly"* *"Technology overwhelming"* *"Lack of training"* *"Cost"* *"Lack of options"* *"Extra work for clinicians"*
Riley 2013: Does telemonitoring in heart failure empower patients for self-care? A qualitative study Aim: To explore the extent to which telemonitoring in	Name: HOME-HF Type: Remote monitoring (Telemonitoring) Setting: Patient's home Duration: 3-6 months Details: Patients in this study used a stand-alone telemonitoring system that required	Sample: 15 patients Sampling: Purposive Data: Interviews Analysis: Constant comparison	<u>Patient +ve experiences:</u> *"Patient-staff communication"* *"Feels looked after"* *"Clinical knowledge"* *"Confidence/ motivation in self-care"* *"Involvement in self-care"* *"Confidence in management decisions"* *"User friendly"*

Study	Intervention	Methods and sampling	Codes generated
patients with heart failure empowers them to self- care Country: UK Funding: National Institute for Health Research (NIHR)	them to take measurements daily using a weighing scale, automated blood pressure cuff and pulse oximeter, and by responding to four symptom questions. This data was transmitted for review by a cardiac nurse in the hospital who responded to clinical change.	Quality score: ++	*"New technology"* *"Flexible"* *"Comfort/ freedom at home"* <u>Patient –ve experiences:</u> *"Reliance on staff"* *"Lack of patient-staff communication"* *"No effect on self-care"* *"Lack of improvement"* *"Not user friendly"*
Sanders 2012: Exploring barriers to participation and adoption of telehealth and telecare within the Whole System Demonstrator trial: a qualitative study Aim: Examining withdrawal or non-involvement in trials, examining reasons people don't participate in some trials. Country: UK Funding: Department of Health	Name: Not stated Type: Remote monitoring (Telemonitoring) Setting: Patient's home Duration: 12 months Details: Telehealth equipment included a monitor unit via which recordings from peripheral devices (measuring blood pressure, blood glucose, blood oxygen level, weight, and peak flow) were to be uploaded to a monitoring centre. Telecare interventions also included various sensors to detect gas, water overflow, falls and movement around the property. Such sensors would trigger alarms direct to a monitoring centre if anything abnormal was detected, allowing emergency intervention.	Sample: 21 patients Sampling: Convenience Data: Observation and interviews Analysis: Constant comparison Quality score: ++	<u>Patient –ve experiences:</u> *"Reliance on staff"* *"Lack of patient-staff communication"* *"Unpredictable clinical management"* *"Lack of improvement"* *"Technical difficulties"* *"Not user friendly"* *"Technology overwhelming"* *"Lack of training"* *"Extra work = tiring"* *"Lack of efficiency/ co-ordination"* *"Cannot replace hospital care"* *"Threat to independence/ control"* *"Technology not needed"* <u>Healthcare staff +ve experiences:</u> *"Change is stressful"* *"Technology not the solution"*
Selman 2015: Appropriateness and acceptability of a Tele-Yoga intervention for people with	Name: Tele-Yoga Type: Educational tool Setting: Patient's home	Sample: 15 patients Sampling: Convenience	<u>Patient +ve experiences:</u> *"Confidence/ motivation in self-care"* *"Involvement in self-care"* *"User friendly"*

Study	Intervention	Methods and sampling	Codes generated
heart failure and chronic obstructive pulmonary disease: qualitative findings from a controlled pilot study Aim: To assess acceptability and appropriateness of the intervention, educational control and study design. Country: USA Funding: University of California, San Francisco, NIHR Biomedical Research Centre for Mental Health, Guys and St Thomas NHS Foundation Trust, and Kings College London	Duration: 1-3 months Details: Home-based one-hour Tele-Yoga classes were offered twice weekly for 8 weeks. Classes integrated held postures, breathing exercises, imagery, meditation and relaxation. The teacher modified postures as needed to meet the physical ability of each participant and offered corrections and adjustments with verbal cues, further explanation, and modelling of poses to participants. Participants were provided with a yoga mat if needed, and encouraged to use common household items as props where necessary.	Data: Interviews and questionnaires Analysis: Thematic analysis Quality score: +	*"Comfort/ freedom at home"* <u>Patient –ve experiences:</u> *"No effect on self-care"* *"Technical difficulties"* *"Not user friendly"*
Seto 2010: Attitudes of Heart Failure Patients and Health care Providers towards Mobile Phone-Based Remote Monitoring Aim: To assess the attitudes of heart failure patients and their health care providers from a heart function clinic in a large urban teaching hospital toward the use of	Name: Mobile-phone based remote monitoring Type: Remote monitoring (Telemonitoring) and self-monitoring Setting: Patient's home Duration: Not stated Details: Patient and clinician views (via survey and interview) of a description of a mobile phone-based remote monitoring system including a prototype system demonstrating the steps they would have to	Sample: 114 patients, 16 clinicians Sampling: Consecutive Data: Interviews and questionnaires Analysis: Content analysis Quality score: ++	<u>Patient +ve experiences:</u> *"Feels looked after"* *"Confidence/ motivation in self-care"* *"Involvement in self-care"* *"Saves travel time"* *"Flexible"* <u>Patient –ve experiences:</u> *"Not user friendly"* *"Technology overwhelming"* *"Unreliable information"* *"Lack of privacy/ security"* *"Extra work for clinicians"* <u>Healthcare staff +ve experiences:</u>

Study	Intervention	Methods and sampling	Codes generated
mobile phone-based remote monitoring Country: Canada Funding: Toronto General Hospital Foundation and the NSERC Strategic Research Network Grant entitles Healthcare Support through Information Technology Enhancements (hSITE)	take for the proposed monitoring system. This included a wireless scale, blood pressure monitor and electrocardiogram. Patients would be required to monitor their own weight, blood pressure, and symptoms daily. Depending upon readings an alert message could be generated and sent to the patient and the clinician via a secure password-protected website.		*"Pro-active management"* *"Encourages patient self-care"* *"Save travel time"* <u>Healthcare staff –ve experiences:</u> *"Not user friendly"* *"Increased workload"* *"Increases errors"* *"Medicolegal concerns"* *"Information privacy/ security"*
Seto 2012: Perceptions and experiences of heart failure patients and clinicians on the use of mobile phone-based telemonitoring Aim: To determine features that enable successful telemonitoring Country: Canada Funding: Toronto general hospital foundation and the natural sciences and engineering research council of Canada	Name: Custom built software on mobile phone Type: Remote monitoring (Telemonitoring) Setting: Patient's home Duration: 6 months Details: Patients were given equipment to measure weight and blood pressure daily and answer symptom questions on a mobile phone. They were also asked to record their ECG weekly using a recorder provided. The measurements were sent from the devices to a blackberry mobile device via Bluetooth, which was transmitted to the hospital server. Instructions or alerts can be sent to the patient, and all information was available on a website. Alerts with new information was emailed to the physician's mobile phone if	Sample: 22 patients, 5 clinicians Sampling: Purposive Data: Interviews Analysis: Content analysis Quality score: ++	<u>Patient +ve experiences:</u> *"Involvement in self-care"* *"Clinical knowledge"* *"Feels looked after"* *"Patient – staff communication"* *"Increased confidence and motivation in self-care"* *"User friendly"* *"Saves travel time"* *"Flexible"* *"Improvement from usual care"* <u>Patient –ve experiences:</u> *"Language barrier"* *"Cost"* *"Lack of privacy/ security"* *"Responsibility = anxiety"* *"Reliance on staff"* <u>Carer +ve experiences:</u> *"Feels patient is looked after"* <u>Healthcare staff –ve experiences:</u>

Study	Intervention	Methods and sampling	Codes generated
	measurements were outside a target range or symptoms reported.		*"Improvement from usual care"* *"Confidence in management"* *"Familiarity/ communication with patient"* *"Proactive management"* *"Encourages patient self-care"* *"Increases patient knowledge"* *"Saves travel time"* *"Better knowledge of patient status"* *"Cost savings"* *"Flexible to practice"* <u>Healthcare staff –ve experiences:</u> *"Cost"* *"Increased workload"* *"Not linked to records"* *"Lack of equipment/ support"*
Sharma 2010: Clinical users' perspective on telemonitoring of patients with long term conditions: understood through concepts of Giddens's structuration theory & consequence of modernity Aim: To understand initial thoughts of clinical users about the newly introduced telehealth service Country: UK Funding: MATCH (Multidisciplinary	Name: Not stated Type: Remote monitoring (Telemonitoring) Setting: Patient's home Duration: Not stated Details: The clinical users participating in this study were involved in delivering care to patients who were taking part in a randomised controlled trial, evaluating clinical effectiveness of telemonitoring of patients with chronic conditions such as heart failure and obstructive pulmonary disease.	Sample: 16 healthcare staff Sampling: Not stated Data: Focus groups Analysis: Thematic analysis Quality score: -	<u>Healthcare staff –ve experiences:</u> *"Increases patient concern/ confusion"* *"Lack of equipment/ support"* *"Lack of training"* *"Increases workload"* *"Slow to change practice"* *"Increases errors"* *"Patient selection decisions"* *"Limits clinical care"* *"Lack of confidence in equipment/ readings"* *"Clinician anxiety"*

Study	Intervention	Methods and sampling	Codes generated
Assessment of Technologies Centre for Healthcare)			
Sharma 2014: Nurses' and community support workers' experience of telehealth: a longitudinal case study Aim: Introduction of telehealth into the healthcare setting has been recognised as a service that might be experienced as disruptive. This paper explores how this disruption is experienced Country: UK Funding: Not stated	Name: Not stated Type: Remote monitoring (Telemonitoring) Setting: Workplace Duration: Not stated Details: Not stated	Sample: 20 clinicians Sampling: Not stated Data: Focus groups and interviews Analysis: Interpretive phenomenological analysis Quality score: +	<u>Healthcare staff +ve experiences:</u> *"Familiarity/ communication with patient"* *"Encourages teamwork"* *"Identifies priorities in care"* *"Improvement from usual care"* *"Technical support"* <u>Healthcare staff –ve experiences:</u> *"Increases patient concern/ confusion"* *"Lack of patient-staff communication"* *"Lack of staff-staff communication"* *"Not linked to records"* *"Lack of equipment/ support"* *"Lack of training"* *"Increased workload"* *"Slow to change practice"* *"Increases errors"* *"Health inequality"* *"Limits clinical care"* *"Lack of confidence in equipment/ readings"*
Stromberg 2002: Interactive education on CD-ROM-a new tool in the education of heart failure patients Aim: To develop and evaluate whether a computer-based program for patients with heart failure was user-	Name: Not stated Type: Educational tool Setting: Hospital Duration: 1 day Details: The final programme constituted eight modules, seven of which were educational relating to heart failure and one	Sample: 42 patients, 3 nurses Sampling: Not stated Data: Questionnaire Analysis: Not specified Quality score: -	<u>Patient +ve experiences:</u> *"Clinical knowledge"* *"Flexible"* <u>Patient –ve experiences:</u> *"Technology overwhelming"* *"Lack of education"* <u>Healthcare staff +ve experiences:</u> *"Familiarity/ communication with patient"* *"Increases patient knowledge"*

Study	Intervention	Methods and sampling	Codes generated
friendly, could be operated by elderly patients and give sufficient information about heart failure Country: Sweden Funding: Aventis Pharma	which was a self-test. After completing the education the patients could perform a self-test which gave a green or red light and results were shown graphically.		*"Automated saves time"* <u>Healthcare staff –ve experiences:</u> *"Lack of patient-staff communication"* *"Not user friendly"*
Svagård 2014: A usability study of a mobile monitoring system for congestive heart failure patients Aim: Usability study of intervention Country: USA Funding: Telemedicine and Advanced Technology Research Centre	Name: The ESUMS system Type: Remote monitoring (Telemonitoring) Setting: Patient's home Duration: 3 weeks Details: Two devices: 1) wearable sensor belt that measures heart rate, activity level, posture and skin temperature 2) a smartphone for viewing and transmitting data to a central server. If the user reaches pre-set activity goals for the day, a "motivation heart" appears on the phone. Also connects with other sensor devices (e.g. pulse oximeter). A pc-application retrieves the data from the server and is used by the supervising nurse or doctor for follow-up from a remote site.	Sample: 5 heart failure patients, 4 nurses Sampling: Not stated Data: Interviews Analysis: Not stated Quality score: -	<u>Patient +ve experiences:</u> *"Confidence/ motivation in self-care"* *"Popular"* *"User friendly"* <u>Patient –ve experiences:</u> *"Not user friendly"* *"Extra work = tiring"* *"Technical difficulties"* *"Responsibility = anxiety"* <u>Healthcare +ve experiences:</u> *"Increases patient knowledge"* *"Encourages patient self-care"* *"User friendly"* *"Better knowledge of patient status"* <u>Healthcare –ve experiences:</u> *"Technical difficulties"* *"Lack of options"*
Taylor 2015: Examining the use of telehealth in community nursing: identifying the factors affecting frontline staff acceptance and telehealth adoption	Name: Not stated Type: Remote monitoring (Telemonitoring) Setting: Patient's home Duration: Not stated	Sample: 105 healthcare staff Sampling: Purposive Data: Interviews	<u>Healthcare +ve experiences:</u> *"Encourages teamwork"* *"Staff education"* *"Automated saves time"* *"Local champions"* <u>Healthcare –ve experiences:</u> *"Technical difficulties"*

Study	Intervention	Methods and sampling	Codes generated
Aim: To examine frontline staff acceptance of telehealth and identify barriers to and enablers of successful adoption of remote monitoring for patients with Chronic Obstructive Pulmonary Disease and Chronic Heart Failure Country: UK Funding: Assisted Living Innovation Platform	Details: Case studies of four community health services in England that use telehealth to monitor patients with Chronic Obstructive Pulmonary Disease and Chronic Heart Failure.	Analysis: Thematic analysis Quality score: ++	*"Lack of equipment/ support"* *"Lack of training"* *"Increased workload"* *"Slow to change practice"* *"Patient selection decisions"* *"Cost"* *"Lack of confidence in equipment/ readings"* *"Clinician anxiety"* *"Lack of evidence of effectiveness"*
Whitten 1998: Nurse reactions to a prototype home telemedicine system Aim: To study nurse reactions to a home telemedicine system Country: USA Funding: National telecommunications information administration	Name: HELP Innovations telemedicine system Type: Remote monitoring (Telemonitoring) Setting: Patient's home Duration: Not stated Details: Not stated	Sample: 4 nurses Sampling: convenience Data: Interviews Analysis: Content analysis Quality score: -	<u>Healthcare +ve experiences:</u> *"Increases patient knowledge"* *"Encourages patient self-care"* *" Familiarity/ communication with patient"* <u>Healthcare –ve experiences:</u> *"Computer Literacy"* *"Not user friendly"* *"Technical difficulties"* *"Lack of equipment/support"* *"Lack of patient-staff communication"* *"Limits clinical care"*
Whitten 2009: St. Vincent's Home telehealth for congestive heart failure patients	Name: St. Vincent Telehome Project Type: Remote monitoring (Telemonitoring) Setting: Patient's home Duration: 1-3 months	Sample: 35 patients Sampling: Convenience Data: Interviews	<u>Patient +ve experiences:</u> *"Feels looked after"* *"Clinical knowledge"* *"Confidence/ motivation in self-care"* *"User friendly"*

Study	Intervention	Methods and sampling	Codes generated
Aim: To study whether telehome health patients exhibit enhanced clinical outcomes and patient perceptions of telehome healthcare Country: USA Funding: Regenstrief Foundation	Details: The telehome project consisted of telehealth devices for patients to record their own weight and blood pressure using electronic scales and blood pressure monitor. Data was transferred via telephone for review by a nurse.	Analysis: Not stated Quality score: -	*"Popular"* *"Comfort/ freedom at home"* <u>Patient –ve experiences:</u> *"Technical difficulties"* *"Cannot replace hospital care"*
Woodend 2008: Telehome monitoring in patients with cardiac disease who are at high risk of readmission Aim: To determine whether telehome monitoring of patients with cardiac disease at high risk of readmission would reduce hospital readmissions, improve functional status, and improve quality of life over usual care Country: USA Funding: Merck-Frosst Canada	Name: Telehome Type: Remote monitoring (Telemonitoring) Setting: Patient's home Duration: 1-3 months Details: 3 months of video conferencing with a nurse, daily weight and blood pressure, and periodic ECG. Video conferences included an assessment of the patient's progress and self-care education by the telehome-care nurse. The educational content was covered within the first 8 weeks of monitoring. All patients were given a 24-7 telephone number to access an advanced practice nurse with questions related to their care.	Sample: 249 patients Sampling: Convenience Data: Questionnaires Analysis: Not specified Quality score: -	<u>Patient +ve experiences:</u> *"Feels looked after"* *"Clinical knowledge"* *"Confidence/ motivation in self-care"* <u>Patient –ve experiences:</u> *"Technical difficulties"* *"Technology overwhelming"* *"Cost"* *"Threat to independence/ control"*
Young 2008: A "basket of care" for heart failure patients managing at home: evaluating a community-based nursing	Name: The Centre Hospitalier—Centre de Santé et de Services Sociaux—Corridor of Service for Heart Failure Patients (CH-CSSS-CSHFP)	Sample: 5 patients Sampling: Purposive Data: Interviews	<u>Patient +ve experiences:</u> *"Patient-staff communication"* *"Feels looked after"* *"Follow up/ co-ordination of care"*

Study	Intervention	Methods and sampling	Codes generated
intervention from a patient's perspective Aim: The researchers aimed to answer the question; What is the patients' perception of care received in the CH-CSSS-CSHFP? Country: Canada Funding: Not funded	Type: Community care Setting: Patient's home Duration: Not stated Details: Community-based nursing intervention is based on six pillars of HF self-care including education, medication, nutrition, signs and symptoms, psychosocial issues, and coordination of health care services.	Analysis: Grounded theory Quality score: +	*"Confidence in management decisions"* *"Improvement from usual care"* *"Comfort/ freedom at home"* <u>Patient –ve experiences:</u> *"Lack of patient-staff communication"* *"Lack of improvement"*
Zulman 2015: How Can eHealth Technology Address Challenges Related to Multimorbidity? Perspectives from Patients with Multiple Chronic Conditions Aim: 1) Identify self-care and health access issues of patients multimorbidities; 2) Identify opportunities to support these patients through eHealth Country: USA Funding: the Gordon & Betty Moore Foundation	Name: Not stated Type: Not stated Setting: Clinic Duration: Not stated Details: Focus groups for the development of a remote care intervention for patients with multiple chronic conditions.	Sample: 53 patients Sampling: Purposive Data: Focus groups Analysis: Content analysis Quality score: ++	<u>Patient +ve experiences:</u> *"Patient-staff communication"* *"Feels looked after"* *"Follow up/ co-ordination of care"* *"Confidence in management decisions"* *"Improvement from usual care"* *"Comfort/ freedom at home"* <u>Patient –ve experiences:</u> *"Lack to patient-staff communication"* *"Lack of improvement"*

2.4.3 Thematic synthesis

2.4.3.1 First order codes

A total of 110 separate primary descriptive codes were extracted from the results sections of the included studies. Where a results text mentioned a similar experience but in the context of a different population e.g. patients vs. carers, it was coded separately for that cohort. There were 47 total codes relating to patients, with 16 positive experience codes and 31 negative experience codes. The most common positive code from patient experiences was “feels looked after” which occurred in 26 studies.[142-153, 156-158, 162, 164-167, 174, 176, 179-181, 183] This code often appeared when patients described feelings of reassurance in being monitored from their home by the remote care technology. The most common negative experience code from patients was ‘technical difficulties’ which occurred in 18 studies.[143-146, 148, 150, 151, 153, 154, 156, 157, 159, 160, 162, 164, 165, 175, 177] This often referred to device malfunction.

Carers had 14 codes in total; 4 positive and 10 negative, many of which mirrored those already existing within the patient experience codes. The most common positive code for carers was ‘feels patient is looked after’ in 6 studies.[144, 145, 149-151, 166] The most common negative code for carers was ‘change is stressful’ in 3 studies[144, 145, 159] – which described the disruption caused by integrating a new device into their caring routine, leading to additional stress.

Healthcare staff codes comprised 22 positive and 27 negative experience codes. The most common positive code was ‘encourages patient self-care’ which occurred in 10 studies[149-151, 155, 160, 163, 166, 167, 174, 183] whereby the remote device incentivised the patients to engage in their own self-care and create lasting awareness

of their condition, improving their clinical outcome as a result. The most common negative code for healthcare staff was ‘increased workload’ in 13 studies[146, 149, 151, 154-156, 161, 166-169, 172, 183] because the extra system for monitoring in addition to their regular practice increased the strain and workload within their environment and this actually hindered their ability to be available for their patients. Appendix 7 shows the first order codes in order of frequency of appearance, and the studies from which they were generated.

2.4.3.2 Second order codes

These 110 initial primary codes were grouped into 30 secondary codes. Patient experiences comprised 11 secondary codes, 5 positive and 6 negative. Carer perspectives comprised 8 secondary codes, 3 positive and 5 negative. Healthcare staff experiences comprised 11 second order codes, 5 positive and 6 negative. These groupings can be shown illustrated according to their user cohort in Appendix 8.

2.4.3.3 Core concepts

Applying the review question to the findings generated a total of 13 inferred concepts; 4 relating to patients, 4 for carers and 5 for healthcare professionals. Due to the associative nature of concept generation, many of the concepts tie together, in particular, those between patients and carers appeared very similar, though the meaning of each concept differed slightly depending on the context. The following are the concepts which have been inferred by the authors from the results and coding process:

Patient engagement with remote care – core concepts

Patient concepts of user engagement revolved around the idea of what the technology provides for the patient that their illness or condition had already taken away. By inferring the reason for the engagement we looked at the limitations imposed on them by heart failure and how technology has helped bridge that gap.

The disease of heart failure lends itself to 3 major limitations to the patient's lifestyle which coincide each with a core concept: Isolation, uncertainty, and freedom. A fourth core concept relates to how technology is seen to fit into the patient's life as a reliable tool for purposes such as self-care, among others.

Isolation

Isolation occurs due to both the limited mobility associated with the condition and the social aspects of a depressed mental state from the burden of chronic illness. This leads to periods of depression, anxiety and loss of contact with their support group. Remote care technologies which reduce the isolation factor fill the gap in patient's lives. By connecting them with their support group once more, providing them with a layer of psychosocial safety netting and allowing them more contact with healthcare providers, patients feel more encouraged and motivated about the technology and their own self-care. This was effectively demonstrated by Heisler and colleagues[182] who found good psychosocial feedback when trialling a peer-support system that connected heart failure patients to each other. Participants emphasized their appreciation of being able to talk to someone who shared similar health issues. As one woman noted:

"I liked to talk with somebody else who had similar problems and share ideas. I felt it was great to share what was happening with me with somebody who knew what I was going through."

Another participant noted:

"I liked that I was talking to someone who had similar conditions to work on."

Another concluded:

"I realized I wasn't alone in this, and that helped a lot."[182]

This highlights the deeper meaning of the disease to the patients' lives as a stressor that they may find difficult to deal with alone, and so tools that allow them to help reduce the burden of isolation will be perceived as a benefit to them.

Uncertainty

Uncertainty for heart failure patients is brought on in many ways. The disease state upsets the order and certainty of their daily lives, by confronting the patient with multiple unknowns that they suddenly need to deal with. Many of these come in the form of not knowing how the disease will progress, what kind of symptoms to expect, and what the disease will mean for their quality of life, and their lifespan. Faced with this, patients will not always know what the best course of action is, how to handle their symptoms, and if what they have done so far is the optimal way to care for themselves. Indeed, some patients may suffer the symptoms of the condition for a long time without even being aware of the diagnosis, as highlighted by Lowrie and colleagues.[183]

In normal practice, dealing with this uncertainty consists of communication with the patient, and providing them with tailored information about managing their condition. Remote care technology can help bridge this gap of uncertainty even further by creating a resource for self-care information, monitoring tools to find out more about the status of their health, and educational materials to find out what to expect, giving them a greater sense of control.[174]

Freedom

Heart failure patients may suffer from fatigue and breathlessness which reduces activity levels and exercise tolerance, increasing the risk of isolation. Furthermore, much of their daily lives may need to be invested in managing their condition leaving less time to themselves to do the things that they enjoy. Therefore technologies can reduce the amount of time required to focus on their condition – this is illustrated by Rahimpour and colleague's[157] remote monitoring solution:

> *The majority of participants agreed that using the (remote care system) could be more convenient than other methods of health care delivery. Less travelling, time saved, and fewer medical visits were identified as useful aspects. One participant said: "To see my doctor can be three hours of wait at times. With this system, it will be much easier for me . . . I think this system is really convenient. I don't need to visit my doctor as often if I have this system installed at home."*[157]

This shows how this kind of remote care allows the patient to gain back some of the freedoms they had lost due to their illness, and give them more sense of control over their lives, without adding extra work and responsibility for maintaining their health.

Technology as a reliable tool

The average heart failure patient is first diagnosed at age 76.[1] Therefore this is an elderly patient population that may often have very little familiarity with new technology, and be slow to adapt new devices or routines into their daily activities. Hence, devices which are able to integrate seamlessly into the patient's already established routines and lifestyle, appeared to garner the greatest positive experience. The ones which sustain the patient's engagement are tools that can be relied upon, last a long time and have very low maintenance. An example of this seamless integration can be seen in Lind and colleagues' study[152] where the intervention involved a pen that transmitted the patient's writing in their health diary to their clinician:

> *(Patients) thought that handling the digital pen was an easy task. "I can manage, 'cause that's nothing special, as long as I can read and hold the pen" (Patient 14).*[152]

This concept, based around the idea of the intervention as a reliable tool, makes a particular task easier than before, with the aid of technology that can be relied upon over a long period of time. A reliable care tool also builds a familiarity with the user over years, until its use becomes habitual. Therefore, technologies which speed up aspects of care that normally take a long time, such as point of care tests instead of full blood tests or remote blood pressure reading instead of home visits, can provide an added incentive for patient engagement. The tool must be robust enough to be used by the patient at any point without difficulty or technical issue, so it must be intuitive, and require little maintenance or instruction. It then becomes an extension of the patient's self-care, rather than an external entity that requires extra effort to initiate.

Carer engagement with remote care – core concepts

These concepts mirror those of patients, though with a slight shift in perspective as observers rather than participants in the effects of the disease.

Isolation

Family and carers of heart failure patients may often feel afraid of leaving the patient alone or worried how they will cope. Remote care can bridge the gap by providing means to look after the patient even when not nearby, and provide reassurance to both the carer and the patient. In one example from Johnson and colleagues, a relative used a remote monitoring device to look after a patient from abroad and follow the health decisions being made by their clinical team.[150] Support networks provided by remote care technology therefore can reduce this burden of isolation in caring.

Uncertainty

Uncertainty can be experienced equally by both the patient and the carers. For carers, a lack of insight into the disease process may lead to anxiety about new symptoms, their clinical significance, and how this impacts prognosis.[144] The anxiety can feed back to the patient and make them more uncomfortable as well. Therefore, technologies which can help answer these questions and manage the expectations of both patient and carer can be extremely valuable.

Freedom

For carers, technologies which increase freedom of the patient, lessen the workload of the carers and the burden that they need to manage in their patient's life, by helping them become more independent. In some cases, use of a remote monitoring device is shared between patient and carer.[151]

The responsibilities of caring can be very time consuming. Technologies and interventions that take extra time to use and adapt to can be seen as adding to the stress of the workload, and increasing the burden of care. These restrict freedom further and can potentially increase anxiety if the intervention does not function properly. On the other hand, tools which free up the carer and allow tasks to be completed remotely, can give back some control to the carer in their duties and make the patient themselves feel well looked after as a result.

Technology as a reliable tool

Carers may feel less inclined to trust an intervention that is not easy to use. Any new system adds an extra layer of work to their duties, and if there are any technical difficulties, it makes their tasks more difficult and causes even more stress. This was shown by Dinesen and colleagues:[185]

> *In contrast to the patients, the spouses/partners were clearly upset if any malfunctions occurred. (…) The question is whether the spouses' emotional responses were related to the illness of their partner or to the anxiety about an unexpected malfunction in the technology. Observations showed that the spouses' emotional responses were linked to the illness of*

their partner, but their feelings were influenced when the technology did not function.[185]

Interventions which are easy to pick up and apply, and fulfil a need which was known to the carer beforehand have a higher chance of being incorporated into their care.

Healthcare staff engagement with remote care – core concepts

The concepts determining engagement for healthcare professionals need to be considered from a very different standpoint. Healthcare staff have two competing yet convergent goals; to provide the best care for their patient, while at the same time providing care to as many patients as they can within a limited time frame. Five core concepts were inferred from within the literature relating to physician engagement: clinical uncertainty, continuous treatment, safety-netting, freedom and time management.

Clinical Uncertainty

Clinicians and healthcare professionals deal with uncertainty on a daily basis, and the practice of investigating and history taking is designed to reduce this clinical uncertainty to narrow down the options for treatments and management of each patient. It therefore follows that any tool that helps reduce this uncertainty further, aids in their role and helps them achieve their primary aim for providing the best care for their patient. In this sense, technologies which can either provide extra clinically valuable information, or otherwise replace an already existing investigation such as blood pressure, by making it quicker and therefore easier to do more frequently, provides information which reduces the uncertainty of managing their patient. An

example from Seto and colleagues shows how remote monitoring could help support clinician confidence and efficiency when managing their patients:

> *Clinicians would be able to monitor their patients closely and would be provided with more information than they previously had to base their clinical decisions on. The information would be particularly useful for medication titration, and could help with false high blood pressure seen in clinic (i.e., white coat syndrome). The alerts would be beneficial to inform them when their patients needed their help the most.*[167]

Continuous treatment

Continuous treatment is a concept which ties into this. Heart failure patients are a population group who often have co-morbidities and it is difficult for each patient to keep up with and enact every piece of medical advice given to them, no matter how beneficial the outcome. The clinician ultimately knows what must be done to treat the patient's symptoms, but often the onus is on the patient themselves to enact solutions such as attending cardiac rehabilitation or maintaining a healthy diet. These examples from Kenealy and colleagues[151] showed how the remote care intervention played a big role in self-care of the patient.

> *"He loves it. He's really switched onto his stats. He's really good. A couple of weeks ago his stats dropped and he phoned and we went over together to see him" (Primary care nurse).*[151]

In addition to encouraging self-care, remote care interventions which can take some of the responsibility away from the patient can ease their burden and improve engagement. For example, an automatic blood pressure monitor takes away the

responsibility from the patient to remember to check their blood pressure daily, or an algorithm which automatically invites eligible patients to cardiac rehabilitation, can free the patient from needing to remember to book an appointment. This type of continuous treatment, assuming the patient engages with the intervention, can benefit the patient, even after the clinician has finished seeing them, and this is seen as a great advantage in terms of raising the standard of clinical care by healthcare staff.

Safety netting

Safety netting, the practice of creating a contingency plan for the patient before they leave the clinic, is an important aspect of the care provided by healthcare professionals when dealing with conditions such as heart failure patients where deterioration can be sudden and recovery is often difficult. Examples of safety-netting practices include making them aware of who to contact in an emergency, or what actions they should take if they suddenly start to feel unwell. It can also encompass booking appointments to 'check in' on patients after a medication dose change. For example, an app which allows contact between the clinic and the patient at any time, can facilitate more rapid and easy 'check ins' with the patient to make sure there are no issues or address concerns quickly. It can also be used to adjust medication doses if problems occur, leading to a rapid early intervention such as in the example of Fairbrother and colleagues:

> *"(Telemonitoring) has allowed me a greater confidence in patients who I thought would maybe not, for example, tolerate a beta-blocker. If they're on telehealth, I might think well, let's have a go because I can daily monitor, I can see the stats there so I would know if they're not tolerating*

the drug; it has encouraged me to be a bit more proactive with medications with some patients." (Professional #3)[146]

This is seen as one of the most vital aspects of a remote monitoring system to clinicians, because it provides reassurance about their decisions in daily practice through an ability to detect any "error" early to avoid serious events of clinical decline. This feeling of reassurance feeds back to the patient, making them feel safer and more 'looked after'.

Freedom

The concept of freedom recurs here as well, but for professionals, they are not limited by the constraints of the disease, but rather by their own resources, such as staff, equipment, medical records and access to rapid investigations. A new intervention can open up more options for the clinician to treat patients in a specific and personalised way. For example a remote care device can give access to a rapid form of renal function testing and give the clinician more knowledge about which medication to prescribe, or an algorithm can pull up patient records from previous GP or hospital visits so the clinician has the most up-to-date information about their patient. A clinician from the study by Green and colleagues[171] recalled how an information network can help speed up ways to identify those that need the most care:

"Another easy, big thing here is that there's a printable recall list . . . We're nowhere near maximizing this management system. We're just doing the real easy, quick stuff, and you can improve rapidly. I saw diabetics that hadn't been seen in the last year. Where are they? You'd think, "how disorganized could you be?" But that's the reality of the

practice. I could go through and just call four or five, just the obvious ones, and they would come in, and I could improve their care."[171]

This kind of system makes the workplace more efficient by utilising available resources in the best way to maximise patient care. Having affordable and easily accessible interventions such as this puts the resources in the hands of clinicians and fills an unmet need that strengthens the quality of their practice.

Time management

One of the difficulties in integrating new interventions for clinicians and healthcare staff, is that their time is already limited due to their current workload, so there is little time to try out new options which could save them time in the long term. Therefore, remote care technologies need to improve time management rather than add to the workload. Indeed, this was the most common concern for new adopters of remote care.

Clinical users recognised the advantages of telehealth, but due to heavy workload were hesitant about possible changes in their work routines because of this service. "there is this change and transfer period ….so during this time having to reconfigure I suppose the way we work will be very difficult"[168]

Remote care systems should not add another layer of data on top of already existing data systems. Automated systems such as algorithms that prioritise the sickest patients based on their blood tests, or automatic appointment systems can significantly reduce workload for staff and potentially reduce the error brought on from fatigue by reducing the number of tasks which do not need complex clinical input. In this way, the remote care can allow staff to direct their attention where it is needed most. If staff spend more

time applying the technology rather than reaping its benefits then it is likely the intervention will be cut out during times of high demand, and this is an important aspect to keep in mind when integrating any intervention.

2.4.4 Themes generated

Having generated all our core concepts and second order codes from patients, physicians and carers, we encapsulated them together into five major themes. Combining them together under these umbrella headings gives us the five critical factors which affect engagement in remote care, and each will be explained in detail in this section.

- Convenience
- Ease of Use
- Education
- Clinical care
- Communication

Having created the themes, we then validated them by checking their appropriateness with our initial first order codes, to ensure that the breadth of the themes captured the entirety of the experiences we recorded. The results of this validation can be seen in Appendix 9.

2.4.4.1 Convenience

This theme was initially known as ‘freedom’ and its positive experiences were associated mostly with saving time or opening new options. Convenience is thus an aspect of the intervention which makes the user’s life easier than the pre-intervention stage, either by time-saving or giving them the freedom to do more, or to enhance their comfort in the current environment.

Patients

For patients, this theme encompassed the second order codes of: ‘adds convenience’, ‘loss of control’ and ‘increased burden of work and responsibility’, along with the core concept of ‘freedom’. (All second order codes are shown in Appendix 8).[143-149, 151-153, 156-160, 162, 165-167, 175, 177-181, 183, 184]

This theme therefore highlighted remote care that increased patient independence. A convenient intervention enabled them to self-care or do things they could not normally do during their day by either saving time in certain activities or by the nature of the technology. Positive experiences from the ‘adds convenience’ second order code included those where the intervention had saved the patient travel time, or had opened up new options for the patient to manage their care at home, and be comfortable in their home environment.[144]

The negative experiences within this theme were associated with extra work and loss of control. For patients, this loss of control often manifested as a new intervention that they needed to rely on, or that threatened their independence, making them more reliant on the staff providing their intervention to carry on with normal life. An example of this is a complex self-monitoring system which takes time away from the

patient's daily activities, and also increased the burden of responsibility left with the patient. This sentiment was reflected in various responses collected by Sanders and colleagues.[159]

> *Responses commonly indicated a strong sense of personal responsibility for health, illness and self-care; and the interventions threatened to undermine such a sense of ' control ' and current approaches to managing health problems: ' I think you feel like you're not in control of your life . . . I just felt that, well, it certainly wasn't for me, and to, from how he explained it, um, you tended to have to do your blood test every single day . . . I try to be a bit more relaxed and . . . I just felt it, it did put a bit more pressure on me . . . you know, holidays or if I had to stay at my mum's, oh God, I've got to come home and do the machine. ' (ID31)*[159]

Carers

For carers, this theme included the second order codes of 'increases stress of care' and 'loss of control', as well as the core concept of 'freedom'.[144, 145, 159] The positive aspects related to opening up options for managing the caring tasks. However, most of the experiential evidence recorded was of negative codes regarding losing control of their tasks and increasing their workload and hence their stress. In the study by Dubois and colleagues,[145] a home-hospitalisation intervention was seen to have detrimental effects on carers, by putting more demands on their care:

> *Caregivers had to support an unusual burden, particularly when patients were confined to bed. Being solicited more often was tiring for working husbands, wives, or aged spouses – H-Hcare was intolerable for some*

> *caregivers. (…) In certain cases, an increase in workload, tiredness, and fear were simultaneously noted during H-Hcare.[145]*

Repeatedly throughout this theme it was found that recurring concepts of workload, responsibility, and stress correlate with each other with regard to trialling a new intervention.

Healthcare staff

For healthcare staff, this theme included the second order codes of 'saves time', 'disruptive to current practice' and 'reduces patient independence', as well as the core concepts of both 'freedom' and 'time management'.[146, 148-151, 154-156, 160, 161, 166-172, 174, 183]

The positive experiences from this theme often leaned towards time-saving for staff, by allowing them to make the decisions they were already making, but in a much faster more efficient manner, freeing them up to do other tasks or see more patients in the same time. An example from Taylor and colleagues[161] showed how remote care technologies can help in understaffed situations to allow nurses to care for more patients in less time:

> *Among all frontline staff, success was described in relation to patient benefits and satisfaction, although for some nurses the productivity gains from reduced patient contact was viewed as a measure of success: We are being asked to see more patients with no additional resources . . . . How can we release a little bit of our capacity? Because our capacity is at absolute maximum all the time . . . I think telehealth helps from that point of view (District Nurse 4, Site A)*[161]

The negative experiences in this theme related to the added workload associated with implementing the intervention. Many clinical staff were also reluctant to change, as new methods were seen to restrict their preferred working pattern.[40] Furthermore, there were concerns about remote care reducing the patient's independence. After using the intervention, some healthcare staff reported that patients had become too dependent on the staff via the increased monitoring and facilities they provided.[149] This increased patient demand could result in clinicians having even less time to spend on each patient, increasing the strain placed upon them.

Overall the convenience theme related to creating more options, and along with that, more time to enact those options. As long as a remote care intervention can improve time management and provide good quality care without being burdensome to use, it is likely to be well received.

2.4.4.2 Ease of use

'Ease of use' was also interpreted as 'interoperability' or 'accessibility' in the early stages of thematic synthesis. In the context of this review, it referred to the technical design elements of the intervention. Particularly, how user-friendly it was and whether any of the design choices enhanced or hindered user experiences.

Patients

For patients this theme included the second order codes of 'accessible design' and 'poor design/ inaccessible to patients' as well as the core concept of 'technology as a reliable tool'. [142-154, 156-160, 162, 164-167, 173, 174, 177, 178, 181, 183]

Patient positive experiences of this included an easy to use intervention, with simple instructions and very few technical difficulties. Patient negative experiences generally involved devices which were intrusive, difficult to use and had many technical difficulties. High costs and unreliability of the intervention were also some design flaws which made the technology 'less accessible'. For example, Agrell and colleagues[142] described a remote care home hub with integrated stethoscope and blood-pressure cuff, which proved difficult to use by sick patients. Often there is a temptation in design to add in more features and functionality to make the remote care more effective. However, if this is done at the cost of usability, the patients may end up much less engaged, and so benefit less.

Given that patients with heart failure comprise an elderly population, many of whom had either poor computer literacy or were not used to technical solutions in their daily lives, they often expressed a lack of desire to interact with basic technology. In designing new remote care moving forward this is an essential consideration in determining engagement with the patient group.

Carers

For carers, this theme encompassed the second order codes of 'accessible design' and 'inaccessible design' as well as once again the core concept of 'technology as a reliable tool'. [144, 159, 173] These codes reflected that of the patient perspective in that the positive experiences centred around technology which was easy to use, (e.g. had a clear user interface) and that had very few technical issues related to its use. As stated previously, much of the negative feedback from carers was related to the stress caused

by technical malfunctions of the device. In addition, design flaws in the technology can make its use difficult, as highlighted by Barron and colleagues:[173]

> *Font and color contrast could be improved for readability. (...) Inactive medications should be separated more clearly from active medications. (...) Vital signs are hard to find.*[173]

Healthcare staff

For healthcare staff, this theme included the second order codes 'accessible design' and 'poor design/ inaccessible to staff'.[146, 149-151, 155, 156, 160, 161, 163, 166-172, 174, 178, 183] The positive experiences for ease of use often referred to a device or intervention which was easy to administrate and explain to patients and staff, or provided information in an efficient, intuitive manner. It also applied to interventions which took less time and effort to install and establish into current practice, such as a patient management system at a GP which integrates remote monitoring into their existing electronic patient records. An example of this was Green and colleagues'[171] clinical decision tool which integrated into current clinical systems effectively and without technical difficulties.

The negative codes from healthcare staff were associated with disruptive design choices such as high cost, lack of security, poor user interface, lack of training with the intervention and unreliable results. An added issue for healthcare staff was the lack of support for remote care in terms of provision of staff and technical expertise to deal with problems.[168]

Technical difficulties are some of the most vital impediments to engaging in remote care, and if clinicians cannot rely on the device for its intended purpose, then trust in

the intervention suffers. Disruptive technology which is difficult to use may require additional staff resources which may not always be available in an understaffed clinical setting. When implementing a remote care technology therefore, care must be taken to consider the resources available and whether the capacity of the clinical environment can fully support the features of the intervention, or if it will simply overtax and burden the staff in their current role. Technologies which can alleviate this and make it easy to install and integrate into current systems, without technical faults, will earn the trust of the staff as they come to rely on it.

2.4.4.3 Education

This theme relates to the educational value of the intervention, namely its ability to provide both the most appropriate information tailored for the user and at the right time for the user to make most efficient use of it. In many cases, this is the main benefit of the intervention, providing users with additional information they would not otherwise have had access to.

Patients

For patients, this theme included the second order codes of 'improves self-care' and 'inadequate patient information', as well as the core concept of 'uncertainty'.[143-147, 149-154, 156-158, 160, 163-167, 173-179, 181-184] Positive patient experiences included those with interventions that gave them effective self-care information and management skills in a way that increased their confidence and motivation to become more independent. The information they obtained was simple and structured in the best way for them to make use of it in their normal lives. For example, a self-monitoring programme that feeds back to the patient about their individual symptoms,

can give patients appropriate and personalised information for their condition and help improve self-care. Easy-to-understand information on self-care such as this was seen as valuable by patients, and helped increase their confidence with managing their condition, which in turn increased their engagement.[174, 181]

Negative patient experiences were where patients reported that the intervention gave no useful information or the information was irrelevant to their current condition, therefore it made no difference to their daily lives. This includes remote care devices which give no immediate feedback to the patient via either the device itself or via clinician contact. Thus patients quickly felt disengaged as a result. This also applied to information websites or electronic health records which used medical jargon, making it difficult for patients to understand.[174]

Carers

For carers, the theme included second order codes of ‘improves education’ and ‘poor education’, and also included the core concept ‘uncertainty’.[144, 151, 173] It is important for carers to learn about the condition of the patient and get to grips with the expectations of the disease progress. It is also important that they are able to access a way to get up-to-date information on the status of the patient. Remote interventions which make this easy for them generated much of the positive feedback. When this information is difficult to access or mired in inaccessible medical jargon, carers shied away from the use of the intervention in favour of other sources.[173]

Healthcare staff

For clinicians and healthcare staff, the theme of education encompasses the secondary codes of ‘empowers patients’, ‘enhances quality of care’ and ‘poor patient education’ as well as the core concepts of ‘continuous treatment’ and ‘time management’.[146, 149-151, 155, 156, 160, 161, 163, 166-172, 174, 178, 183] The theme centres on the informative value that an intervention adds to their current practice. Positive experience involved interventions that provided appropriate guidelines or clinical suggestions to aid and save time in the management of specific patients. Clinicians also identified the educational benefit of remote care on self-care habits of patients:

> *Staff agreed that telecare helped patients understand their condition and communicate better with health professionals. “(telecare) is a catalyst for quite rapidly increasing people’s (health) literacy” (Primary care manager).*[151]

In this way, educational ability of any new remote care intervention helps raise the clinical standard of treatment and involve the patient in their own management. This also falls into the category of providing a continuous benefit to the patient, which is highly valued by healthcare staff. In addition, providing extra educational resources helps offload the task from the clinicians, which fits in with other factors for engagement.

By contrast, the negative healthcare experiences of education involved both insufficient/irrelevant clinical information and also poor education provision to patients.[146] Since it is recognised that patient education is one of the main advantages for a remote care system, healthcare staff will be wary if this aspect is missing. An intervention which does not provide feedback or allow patients to be

updated on their health status, provides little motivation for both using the device and in improving their self-care, and this has a knock-on effect on healthcare staff perceptions of the usefulness of the device.

2.4.4.4 Clinical Care

This was a very clearly defined theme which involved either improving or hindering the current clinical care provided for heart failure management. In most cases, the effects of this theme could be measured and observed in terms of patient outcome over the long term.

Patients

From the patient perspective, this theme included the second order codes of 'improves clinical care' and 'does not contribute to care'.[142-153, 156-159, 162, 164-167, 174, 176, 179-184] Positive experiences involved an improvement over current care in terms of better symptom control and general confidence in the management plan provided. Patients often commented that certain remote care interventions made them feel more 'looked after' once they were aware that their measurements were being monitored from afar.[146] Negative patient aspects involved trouble integrating the new system into their daily lifestyle, causing a disruption in co-ordination of their existing care. Some patients felt that the intervention had no effect on their symptoms or the level of their care and that the technology was ultimately not needed.[152]

Carers

For carers, this theme includes the second order codes of ‘improved care’ and ‘technology not needed’.[144, 145, 149-151, 166, 173] Much of the positive aspects for carers in this theme are focused on the fact that they may feel more supported using the intervention than without it. In this way, the reassurance of the extra clinical support helps them perform their task and make sure that more care is being provided for the patient, so that they need not struggle alone.[144] In some cases, having the clinicians involved with the patient and providing the remote care intervention allowed the carers to gain better support, both clinically and socially.[173]

On the other hand, negative aspects of clinical care from a carer’s viewpoint were found often to be from patients who already had sufficient care to meet their needs, in that the additional intervention became superfluous. Additionally, there were cases where the patients were too sick to be under an automated monitoring system and required personal supervision. Adding to that the mistrust of the carers of the technology would introduce an extra level of stress to the current care environment.[159]

The considerations for choosing remote technologies appear to differ greatly between patient and carer, and much depends on the current care of the patient themselves. This needs to be evaluated in context to their specific needs to see whether the carer would benefit from using the intervention in their task, or whether it would be a hindrance.

Healthcare staff

For healthcare staff, the theme incorporates the second order codes of ‘enhances quality of care’, and ‘does not improve clinical care’, and the core concepts of ‘clinical

uncertainty', and 'safety netting'.[146, 149-151, 155, 156, 160, 161, 163, 166-169, 171, 172, 174, 183] Positive clinical care aspects involved being able to administer guideline recommended management more reliably and with less error over a wider scale, which improved the overall standard of their care. Additionally, a great clinical benefit expressed by clinicians was the ability to be pro-active with treatment. Often the increased frequency of monitoring patients allowed the staff to pick up deteriorating health much quicker and intervene early in order to prevent a worse outcome. This improves the safety and quality of management by providing an extra layer of security and also fulfils the 'safety-netting' criteria which was found to be very valuable.[146] The benefit of this is that it bridges the gap in primary and community care, where heart failure patients are rarely seen frequently and may have periods of long stability, but may be at risk of sudden deterioration; the regular patient monitoring helps provide reassurance to both patient and staff involved.

Negative aspects of clinical care for staff were equally impactful. They involved interventions which disrupted current management, often by giving unreliable, incomplete, or false information, or simply did not make a difference in the daily management decisions, or patient outcome. In the example by Sharma and colleagues,[168] the remote care offered basic features such as home BP monitoring, but it did not provide the information that clinicians needed to know to make a full assessment, such as whether the patient had an infection. This raised concerns that if remote care was to replace clinic visits, there would be large gaps in the daily care of these patients due to these missing features. These perceptions led to a feeling that the technology may hinder usual care, and disrupt the current 'face-to-face' care that patients are used to.

Clinical care is a vital part of any remote care assessment, and it needs to be assessed in context to both the needs of the patient, their current care, and the resources available to the staff. This means that the effectiveness and engagement of a particular remote care device is situational to the environment, and the gaps in clinical care, where technology could make a difference.

2.4.4.5 Communication

The final theme recurred in all cohorts of remote care discussions in both a positive and negative light. The communication theme encompasses the quality and frequency of interpersonal contact involved with the intervention.

Patients

From the patient perspective, this theme included the second order codes of 'improved communication', and 'poor communication', as well as the core concept of 'isolation'.[142, 144-146, 148-153, 157-159, 165, 166, 174, 176, 179-184] This often meant the frequency with which they remained in contact with their nurse or doctor. In general, patients favoured human contact from healthcare staff and felt more reassured by it. Therefore interventions which facilitated this were seen to be more appealing.[142]

> *The patients had constant contact with the HF clinic and their healthcare professionals via the daily transmission of BW. This constant contact was perceived by the patients as receiving good care from the HF clinic.*[153]

Comments from patients also indicated that greater human contact helped with their feelings of isolation, and encouraged them to self-care. This feeling of being able to communicate more frequently, ask questions, and interact with staff and other patients, made sure that the remote care intervention was seen as valuable and worth the investment. In addition, patients also liked interventions that could connect with their family and friends for further support in case they needed it. There were also some social interventions that connected patients with each other and these showed widespread approval within this heart failure cohort. Often with a chronic illness that reduces mobility, it impacts the social activities of the patient so it is not surprising that this element can often be overlooked with these interventions.[182]

Conversely, many of the remote care interventions by their nature led to reduced contact with physicians due to their automated processes. Often patients found that they missed the human contact element of regular clinic visits. Rather than having a device to provide information for them, they preferred being able to ask questions from staff members directly.[142]

When this human contact element was taken away, some felt more distant and perceived that something was lacking from the consultation. While remote care may obtain information efficiently, sometimes human contact can be more reassuring and have a bigger impact on patient engagement.

Carers

For carers, the theme of communication encompasses mainly the core concept of ‘isolation’, which is expanded on in section 2.4.3.3. This mainly revolved around the feeling of fearing to leave the patient on their own. Hence, the ability of remote care

to mediate communication between both the patient and healthcare staff was seen as valuable and reassuring to carers.[150]

Healthcare staff

For healthcare staff, this theme of communication includes the second order codes of 'improved communication', and 'poor communication', as well as having some relevance to the core concept of 'safety netting'.[146, 149, 151, 155, 161, 163, 166, 168, 169, 171, 174, 178, 183] Healthcare staff are often concerned with both contact with patients and also the connection with other specialists that can aid the treatment. A positive communication experience with other staff members is found in interventions which connect multi-disciplinary teams together seamlessly to improve patient care so that each member of the team is aware of the plan, which in turn encouraged teamwork.[161] Regarding staff to patient communication, healthcare staff felt that with more frequent contact, they gained a better awareness of the patient's tendencies and are able to make better decisions on their care, earlier.[151, 155]

The increased availability of communication with patients via remote care was felt to increase trust between the staff and their patients and these comments show that staff felt their patients were more open to them. This fosters a good clinical environment, especially in the management of chronic disease, since the familiarity gained by clinicians from the patient is vital to detecting early deterioration, and also motivates both parties to continue to use the device, for reassurance and safety-netting.

Negative staff experiences with communication in healthcare staff included systems which did not connect with other members of the team, or caused a disruption in teamwork, reducing the effectiveness of care. An example was a remote monitoring

system which provided the GP with extra information but was unable to send this information on to heart failure hospital consultants, and thus made referrals harder.[146] Staff also found that interventions that reduced interaction with patients received much less support from both parties. With the nature of remote intervention limiting face-to-face time, it created a sense of distance with the patient, which was concerning to some staff.[146]

Overall, communication is a vital part of any medical consultation, and is often taken for granted. This aspect is made especially clear when communication is reduced by these interventions, leading to a palpable gap in the care of the patient. Remote care interventions which acknowledge this and allow for further communication to take place, both between patients and staff and between peers, create the foundation for a positive and co-ordinated care environment.[149]

2.4.5 Health inequalities

Part of our aim was to consider the impact of remote care technology on clinical care in terms of equity of access. It is important to keep these factors in mind as it would affect the way that remote care is distributed, and its engagement within neglected patient cohorts who may need it most. When looking at the data of interventions and the population it was used on, various health inequality issues became apparent. This section details these findings from the data in terms of usability, patient selection criteria, demographic distribution and the widening inequality gap brought on from the implementation of remote care.

2.4.5.1 Usability

As mentioned in the 'ease of use' theme, there are various factors which may hinder the accessibility of interventions to a disabled population. In this heart failure cohort, allowances need to be made for patients who have visual impairments or problems with dexterity.[167] These conditions are common, especially in an elderly population, and if the design of the intervention does not take this into account, it can result in excluding the patients that might have benefitted the most. These accessibility options, which sometimes are overlooked, are very important to capture the wide range of patient populations with heart failure. Riley and colleagues[158] recount an example of one such patient who struggled to use a remote care device, leading to undue stress:

> *a 74-year-old man, who was registered blind and whose mobility was severely restricted by Parkinson's disease, used the start time of a daily television programme as a reminder to use telemonitoring. Despite his poor manual dexterity and limited vision creating some problems, he persisted in his use of the equipment: 'I keep losing the finger contact and because of my sight I have to search hard to find it and that unfortunately sends my blood pressure up and then I have to redo the test.' (Edward)*[158]

In addition to co-ordination and visual problems, some patients were unable to use a weighing device because it required them to remain standing for several minutes.[150]

2.4.5.2 Patient selection decisions

With any new interventional trial, an inequality may arise between patients who do and do not have access to the interventions. This is often at the behest of the clinician, who needs to decide which patients are more suited to the intervention than others.

Due to this, a gap in clinical care is created whereby those patients chosen subjectively are potentially afforded increased care compared to other patients at the same practice. This is confounded by the baseline health inequality of patients who do not present to the GP on a regular basis and thus fall below even current care standards. The weight monitoring intervention in the study by Johnston and colleagues[150] demonstrated this selective service based on clinician opinion, creating a defined cohort of highly monitored patients above those of current care.

> *Some nurses were found to 'cherry pick' participants, one commenting 'I know (this patient) would not comply.'*[150]

It is often the case that, with limited resources, it is difficult to provide the same technological assistance and support to each patient who might need it, and this leads clinicians to set up their own criteria for prioritising patients based on need, such as they do with other treatments.[146]

Over a short intervention trial period, it seemed that some clinicians felt that monitoring was not useful in patients they deemed stable, and were thus less inclined to offer the intervention to them. While it is important to effectively utilise resources for maximum utility, it may lead to situations where patients are only provided with remote monitoring once deterioration of their condition occurs, far beyond the point where the monitoring may have been effective to prevent this deterioration. This may run counter to the intended design of the interventions to begin with. Therefore, any trials of such interventions should consider the predicted use-case in areas where resources are limited, and the impact this has to the current inequality gap.

2.4.5.3 Demographic representation

During any intervention trial, the criteria on which patients are given the new remote care intervention or not are often decided a priori by the research group. Observing the demographic trends from included studies (Appendix 5) shows a distinct preponderance to Caucasian ethnicity and male gender. In addition, there is generally poor reporting on religion, socio-economic status, social capital, disability and vulnerable groups. It is therefore difficult to assess the impact of remote care integration on more disparate groups within populations. If these trials are representative of the use of remote care, it may indeed create a widening health gap, as those with greater links to healthcare are given more opportunities to be cared for, whereas those not included in such trials are excluded from this greater level of care.

2.4.5.4 Widening the inequality gap

There were some experiences of clinician anxiety regarding the widening health gap created by technology. In the study by Earnest and colleagues,[174] some clinicians highlighted this as a concern of implementing remote care, and were worried about how it would translate in areas with fewer resources.

> *One was concerned that it might exacerbate disparities in care, noting that such systems are more likely to be used by socioeconomically advantaged patients and may lead to those patients claiming a disproportionate share of the doctors' time.*[174]

This certainly is a valid concern where resources are stretched, and inequalities already exist. Many remote care interventions take the form of highly technologically advanced, expensive devices, which, while rich with clinical data, are prohibitive for widespread use in terms of costs and resource drain. It is worth noting the impact of

these interventions on the rest of the clinical care of the population, whether it creates a wider benefit to the whole, or simply allows greater monitoring for those who have the most care in the first place.

2.5 Discussion

2.5.1 Limitations

The limitations of this study can be categorised into those of the methodology, those of the studies selected, and those of the phenomenon studied.

2.5.1.1 Limitations in methodology

The process of qualitative synthesis is a subjective endeavour. Although we have attempted to mitigate bias via means of double-coding, cross checking, and using established qualitative methods to extract data, the end result is a product of subjective reflection. This may, unknowingly, mirror the pre-conceptions of the authors, and it is by presenting the data extracted to its greatest extent, that we can perhaps provide the right context to frame these conclusions.

Grounded theory

Grounded theory processes exist to attempt to construct a 'blank-slate' perspective of the phenomenon, by reducing the amount of a priori pre-conceptions to a minimum. Due to this, the current paradigms of user engagement with health technology, such as the unified theory of acceptance and use of technology (UTAUT2)[186] and the technology acceptance model (TAM)[187] were not used in the development or

construction of the themes. Nor do they input into the recommendations from this review. As a result, the reviews which have previously explored the area of user engagement, which may have found findings that are different or even opposed to this review, have not been considered in the final model. This was done in an attempt to reduce the bias from the subjectivity of the analysis, but as with any grounded theory study, it comes at the cost of creating findings which are far removed from current conventions of thought in the subject matter.

Line-by-line coding

While line-by-line coding is an established practice for extracting data for qualitative analysis, its specific form is relative to each author. Within each extract there are wide variations in both length and relevance of texts extracted. Some lines may further have a double-meaning, fitting into multiple codes. The subjectivity is manifested in the decisions of when to split meanings into separate codes, or combine lines into one unifying first order code. Such a decision was made, for example, in splitting the codes 'involvement in self-care' with 'motivation for self-care'. We found many examples of experience relating to self-care from a patient's perspective, but judged that the 'feeling of being encouraged to self-care' can be clearly delineated from the action of 'actively taking part in self-care' although the two often overlapped.

Core concepts

As previously illustrated, the answers to the questions in the objectives have been inferenced from the codes created and the included texts that have been studied by the authors. The interpretation is made in context of these studies, and again, without

reference to external theories. However, the reviewers' reflexivity may come into play in the wording or actualisations of the core concepts. This is mitigated to some extent by combining the concepts with second order codes to achieve a more objective interpretation of the theme; however this reviewer bias should be acknowledged and even accepted as part of the qualitative process.

2.5.1.2 Limitations in studies

Quality

The studies included were of a wide range of different methodological and analytical quality. This has an impact on the codes that were generated, as first-order codes from poor quality studies may be subject to greater variability. We have tried to take this into account by listing all the studies from each code, and identifying the quality of the studies they were sourced from (Appendix 7). Of course, the overall themes may well have been different if only the high quality studies were included. At the risk of missing useful information and coming up short of the point of saturation, we have included all qualities of studies in this review.

Sample size

Many of the studies included were small, sometimes with only 5 or even 2 patients. Opinions gained from these studies are unlikely to be representative of the whole population, and so the weighting of the experiences would be less than a study with greater sample size. The wide range of study sizes may skew the experiences towards those which are mentioned in these small sample sizes, as it increases the frequency of

appearance of the related codes. We have listed the sample size of each study in the characteristics of studies table (Table 2.1).

Intervention types

Defining remote care is an arbitrary task, which necessitates inclusion of a variety of different interventions. While many of these have overlapping characteristics, they are all individual and unique. Therefore, patient experiences regarding a specific intervention does not always translate to each remote care device. The experiences need to be taken in context of the remote care they were exposed to. A summary of each intervention is included in Table 2.1 to establish this context.

2.5.1.3 Limitations in phenomena studied

First degree bias

As mentioned, the researcher's reflexivity plays a role in the overall generation of the themes, which is based on their core concepts as well as the grouping of the second order codes. This process happens both inductively and intuitively and it cannot truly be distanced from pre-conceptions and beliefs of the reviewers themselves. Rather, through continuous revision of the studies, the immersion helps provide a viewpoint that is grounded in the evidence extracted, albeit subject to reviewer interpretation.

Second degree bias

While the process of qualitative synthesis is far from objective, the same can be said for the qualitative primary studies from which this review is based. The authors of the

included studies have had to face the same constraints of bias and pre-conceptions, which inevitably alters the characterisation and appearance of the study as it is published. This differs based on the method of the analysis, pre-conceived notions of the authors, and the rigour of the study. This then has a large impact on the emphasis of each experience within the study, which leads to the experience being extracted in a certain way, by the authors of this study, translating them into first order codes, which are, in effect, subjective interpretations of the authors of the individual studies. That being said, the findings from the experiences of users have been triangulated throughout multiple studies in order to be interpreted into the themes generated. The examples and quotes in the results may identify certain individual aspects, which are part of a greater whole perspective of technology experience. Therefore, while individual papers and study findings may be highlighted to accentuate a particular theme or core concept, the breath of our review has allowed such findings to be backed by others within the same remit, and thus robustly encompass a wide breadth of user experience. The validity of triangulation of first order codes from multiple sources thus ensures that the experiences captured are shared amongst a variety of locations and demographics, to make the findings more generalizable, despite the second degree biases engrained within individual studies.

Third degree bias

Taking this further, the experiences recorded by the authors of primary studies are based on the subjective answers of the remote care users involved. These transcripts are subject to numerous cognitive biases that mean that they may not be representative of the user's true experience. For example, confirmation bias from users that are reluctant to use a device *a priori*, may appear in the form of mistrusting technology,

leading preconceptions to colour the experience rather than providing accurate feedback about the attributes of the technology itself. This is also a reason to limit the target population in this review, by focusing on heart failure, and the patients and staff that face it, the context of the study is clarified, such that these preconceptions can be normalised in the experiences gathered.[188]

2.5.2 Recommendations for future remote care design

Using these five generated themes, we can start to develop guidance on the optimal design of remote care technology for user engagement. Each of these elements is a key factor on whether a user continues to use the intervention or ultimately ends up discarding it.

2.5.2.1 Convenience

The remote care intervention must be shown to provide a benefit in either the comfort of the user or demonstrate a time-saving aspect which has significant impact on their daily lives. In many ways this means that the user is able to carry out the tasks they would normally be expected to pursue, whether it be a patient's self-care or a clinician's daily reviews, but in a more efficient manner, or in a location more convenient for both parties.

2.5.2.2 Ease of Use

The intervention should be tailored with the user's experience in mind. For elderly heart failure patients, this means a simple and intuitive interface, with very little or no

technical knowledge needed, and aspects of their care clearly defined and highlighted by the intervention. The closer the intervention comes to a normal daily activity, the more seamless the transition towards its use. This is also important for clinicians as user interfaces must be clear and without overt complexity, but should have the ability to provide all the necessary information in an efficient manner which lends itself well to the clinical decisions that need to be made. Therefore, the design of such interfaces needs to be made from a physician's perspective in mind.

2.5.2.3 Education

The educational capability of an intervention often defines its usefulness in this setting. The intervention must be shown to provide a demonstrable insight to patients, providing information in a relatable way that is specific to their situation. This way, it should aid patients who want to self-care and motivate them to find solutions to their symptoms, to increase their sense of control and self-reliance.[189]

For healthcare staff, the educational aspect is perhaps more vital. It is often challenging to keep fully up to date with the best standard for the treatment of heart failure. Therefore, the intervention should help to keep up with current guidelines and recommended practice. This can also refer to providing frequent patient monitoring information and aiding clinical decision making. A remote monitoring device which measures health status should be understandable and usable by all healthcare staff from community nurses to heart failure specialists. An effective educational component of a remote care intervention both informs and supports clinicians to carry out best practice.

2.5.2.4 Clinical Care

While clinical care is often seen as the most significant aspect of the operational success of a remote care device, it is but one of the many facets of user engagement. For patients, the aspect of clinical care more often refers to the perception of greater care, rather than the effectiveness of the care itself. This means that greater value is placed upon more frequent feedback, contact with clinicians, and impactful changes to their lifestyle brought on by the intervention and the information it provides. If the intervention demonstrates that the patient is somehow being monitored constantly or that more attention is being paid to their well-being, it will foster a sense of being 'looked after' which ultimately encourages the perception of better care.[182]

For clinicians and health care staff, clinical care is perhaps the primary aspect they will examine when deciding whether to initiate or fund an intervention in their practice. Often this is based on evidence-based outcome studies using the intervention. Therefore, a robust series of clinical trials that demonstrate the clinical value of an intervention is vital in order to inform and justify these funding decisions. Beyond this, clinicians will prioritise the interventions with maximal clinical outcome in order to make the greatest impact on patient health. In managing resources, they would also consider whether the intervention itself fills a gap in the service provision which they would ideally like to provide. Often, it is difficult to change an established pattern of work, and therefore adding a feature to clinical practice where none is warranted may end in staff non-engagement. However, unmet needs remain, and identifying and allowing practices to recognise this need may go some way to shifting resistance to change that is prevalent in current medical practice.

2.5.2.5 Communication

Communication may be an overlooked factor, since the nature of remote technologies allows automated information transfer, and the idea of efficient time management sometimes necessitates fewer contact sessions between staff and patients. However, in this patient population a more traditionalist trend was found where value is placed on contact time with a responsive member of their healthcare team, be it face to face or via remote connection. The reassurance gained from this contact appears to be vital for patient engagement, as little contact can leave patients feeling anxious and disconnected from their care.

Therefore, remote care devices need to demonstrate some form of flexible two-way feedback between the staff and the patient, allowing patients to communicate their needs and issues to the clinicians administering the intervention and also allowing the staff to send messages or be in regular contact with the patient's environment. Additionally, many patients value the option of having remote care to connect to their friends, family, carers, and support network in general. Communication with other patients also had some psychosocial impacts on patient mental wellbeing. Therefore, in an isolating illness like heart failure, patients will turn to new technology to overcome this limitation and seek to connect with others in their daily lives.

From the healthcare staff perspective, communication between team members is vital in order to co-ordinate both the new intervention itself and the ongoing complex care and management which these patients require. Many of the patients will be elderly and have multiple co-morbidities necessitating a complex regimen of medication and outpatient health services to maintain their daily wellbeing. Too often, the flow of patient information between these services becomes lost or confused, relying solely on the patient and their family to carry information between specialists. This is a trying

limitation and one where remote care is equipped to deal with, not only with the care of these complex patients but within healthcare professionals' daily practice in general. This touches upon a wider issue whereby referrals and interdisciplinary services are difficult to co-ordinate between staff shortages and system incompatibilities. Therefore, an integrative mechanism in remote care is highly valued and can help the healthcare standard as a whole.

With regard to contact with the patient, while this was not perceived by staff to be as valuable as it was from the patient perspective, it still carries merit as further exposure to the patient's lifestyle allows the clinician to make better care decisions and reach a more appealing outcome for the patient, which in turn gives the impression of better care from both parties.

2.5.3 Implementation of remote care within clinical trial design

Based on our observations of studies with remote care devices, we noted certain practices that need to be carefully considered in the future when trialling a remote care device.

First, to ensure a representative sample of the population, as with any clinical trial, care must be taken to distribute the intervention in an area with a diverse ethnographical population to assess the effect of the intervention on different population groups. Those who have trouble with English, or those with disabilities, who might not be able to access medical services normally, can fall through the gaps and therefore create a study which is biased towards a certain population. The same diversity should be achieved in proportion of patients from each gender, and, where possible, different socio-economic backgrounds.

Second, we found that recorded experiences from users my both contrast and contradict each other, even within the same study. As an example, Hall and colleagues[165] show that some patients were excited by a new technological device, but others were overwhelmed with technology from the intervention, which led to both positive and negative feedback relating to the same factor. A smaller sample size therefore would be insufficient to obtain a clear picture of the effect of the intervention on the users. A large sample made up of different ages and backgrounds may provide more detail without isolating the experience to a small user group.

Third, as mentioned in the health inequalities section, the selection of suitable patients for the intervention will make a great impact on the results obtained. Sometimes patients with extremes of the condition may be selected or selectively excluded by the clinicians which may lead to a bias in the perspectives obtained. When patient experience is the main outcome, it is important to obtain a sample that encompasses as much diversity as possible, in order to encounter the greatest amount of adversity to implementation early on.[189] Without an inclusive sample, there may be user-related issues that are overlooked at the trial stage, which could have repercussions in future developments of the technology.

Fourth, when evaluating user experiences, it is useful to consider both the patient and healthcare staff viewpoint in the same study. This gives a good estimate as to how readily staff were able to use the intervention, and the impact that it has on their current care. Taking the patient or healthcare staff perspective alone, may overlook those issues related to the excluded party, which may ultimately prevent implementation in the first place.

Fifth, the current workflow in the NHS is centred round an escalation system whereby patients are treated in the community until their condition is severe and requires referral to secondary or tertiary centres, or otherwise hospital admission. Each of these escalation steps involves closer contact with healthcare services and more stringent follow up. It is important therefore to know where the new technological intervention will fall within this established structure, and therefore predict where it will have the most impact. This will affect who oversees administering the device, and to which cohort of patients. It also affects which electronic systems the intervention would need to link up to, be it GP systems, or hospital-wide networks. Interventions which do not consider the gaps in current care may create more disruption for staff as they attempt to navigate their normal work routine while adding additional steps required to use a device that does not compliment nor aid their current care environment.[159]

Finally, in a few cases, patients and staff had negative experiences which were external to the technological device itself, and rather about the third-party support provided around the device's use. This is not intrinsic to the device, however, and could be improved with effective trial planning. In the study by Sanders and colleagues,[159] additional help in the form of support staff and engineering expertise was promised to clinics to support the intervention, but was never achieved, leading to a poor opinion of the device. Similarly with Odeh and colleagues,[155] staff and patients were forced to wait for service technicians to conduct the home installations, which delayed the use of the device and caused added frustration. Therefore, planning a support network to facilitate smooth administration, installation and application of the device is essential for trial management. If these networks become an issue in themselves, then consideration should be taken as to whether the area is appropriate in introducing a

new technological intervention, where the infrastructure is not in place to do so effectively.

2.6 Conclusion

The aims of this review were to establish the core attributes of remote care technology that lead to effective engagement with users, be it patients, carers or healthcare staff. Figure 2.2 summarises the key themes obtained from this study and the meaning applied to each user group within them, which show practical ways of designing remote care for user engagement.

While this has been a qualitative analysis, subject to the interpretations of the reviewers, the commonalities between user experiences has been very cohesive within our identified attributes. The concepts of clinical care and education are often at the forefront of any assessment of these new technologies when deciding on whether to invest the resources required for initiation. Our study suggests that overlooked factors such as communication, ease of use, and convenience for the user have a significant role in determining engagement of users and ultimately deciding whether the technology will be successfully adopted long term. Technology designers creating remote care for heart failure patients would benefit from emphasising these aspects within their intervention while keeping in mind the differing perspectives of patients and professionals.

Overall these aspects are not always seen in isolation. The nature of the remote care intervention is to interact meaningfully with the user and thus instigate a change in the self-care of patients, or in the working practice of healthcare staff. It will often be the

case that the increased communication brought on from a remote care intervention leads to a perception of greater care from the patient, which leads to improved feedback to the clinician and an effect of improved perception of the devices' educational and clinical aspects. Likewise, convenience can be an important component contributing to ease of use. Successful and engaging intervention design should therefore try to manage this perception correctly by combining these facets together in the appropriate way to meet the user's needs.

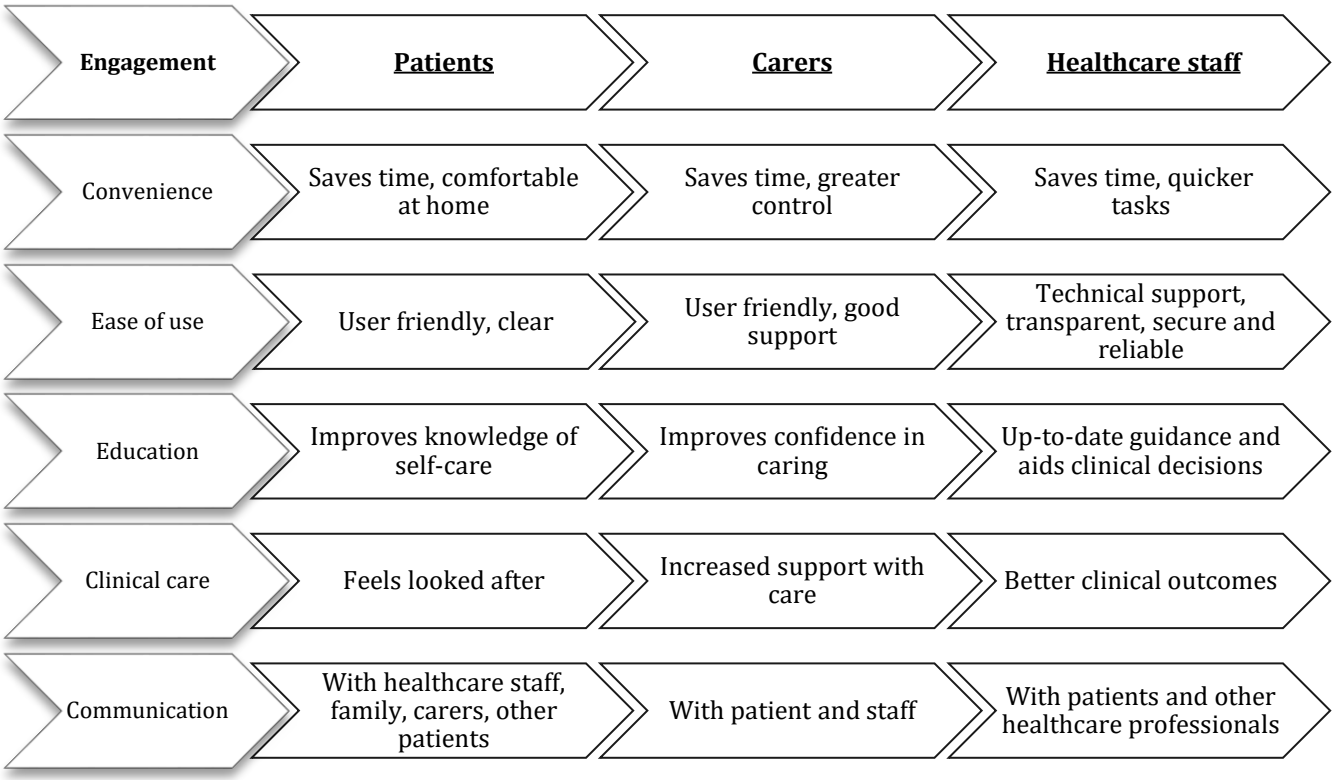

Figure 2.2 Final thematic map representing the key points of each engagement theme and what they mean to each user group.

CHAPTER 3

PATIENT PREFERENCES FOR USING REMOTE CARE TECHNOLOGY IN HEART FAILURE: A DISCRETE CHOICE EXPERIMENT

CHAPTER 3: PATIENT PREFERENCES FOR USING REMOTE CARE TECHNOLOGY IN HEART FAILURE: A DISCRETE CHOICE EXPERIMENT

3.1 Introduction

Remote care technologies are designed to help clinicians gather clinical data from patients remotely, which would allow for closer monitoring in patients who are at high risk of day-to-day clinical variation. The potential benefits of remote care as well as the drawbacks of lack of user engagement have been explored in detail in the previous chapter. Following on from the findings of the systematic review in Chapter 2, which identified the common themes in the experiences of users when engaging with remote care technology, a way to assess these themes quantitatively was sought. This chapter outlines a prospective choice-based survey which aimed to gather the preferences of patients with heart failure in relation to remote care technology, using these common themes.

Choice-based surveys have often been used to evaluate the effective 'stated preference' of a population for health provision. These methods have been widely tested in the domain of health economics, where such evaluations become the crux of government incentives in distributing limited resources for maximal effect. Two of the most common patient-facing methodologies in this domain are the contingent valuation method and discrete choice experiments.[190]

The contingent valuation method is used in health economics research to determine how much participants would be willing to pay for specific health services. In survey terms, it may involve questions that ask participants to put a monetary value on different health service options, as described by hypothetical situations. This is useful for finding out the willingness of participants to pay for specific health aspects, in relation to each other, and determining their stated need. The difficulty with this design

is that it is prone to bias – if the hypothetical situation is too far removed from reality, then the results of the survey will not match actual willingness to pay.[191, 192]

Discrete-choice experiments involve a questionnaire design whereby certain variables of interest known as ‘attributes’ are traded against one another in various scenarios in order to ascertain the importance of each variable relative to each other.[193] The design process is well established in the literature and it provides robust evidence on respondents’ stated preferences, which can be used to inform the design elements of future remote care technology.[194] The questions are carefully constructed to allow participants to weigh up each attribute against each other, thereby creating a ranking of ‘utility’ or usefulness of each attribute to participants, which is a measure of relative importance.

Since we were less interested in discovering the relative monetary value of each theme, but rather, the relative effect of each theme on patient engagement, the discrete choice experiment was utilised for our study. The themes were designed such that the meanings had minimal overlap and thus were independent enough to be clearly delineated in questionnaire form, which lent itself well to a choice-based survey.[141] This questionnaire design allowed us to gather primary opinions from patients using the themes discovered in chapter 2.

The 5 themes were:

- Communication
- Clinical Care
- Education
- Ease of Use
- Convenience

Thus the goal of this questionnaire was to analyse these 5 themes using real patient responses, using a discrete choice experiment (DCE), to quantify the relative importance of each theme in the use of technology. The reason for ranking the importance of each theme in this manner is to help technology designers to understand which features to prioritise in the design process in order to enhance user experience and engagement. This will provide evidence to support the development of more engaging and acceptable remote care technologies for the future benefit of this chronically ill and ageing population.

3.2 Methods

In order to design this discrete choice survey, we needed to set two principal parameters of the questionnaire; the 'attributes' and the 'levels'. Attributes are the actual factors on which the patients would need to make choices. In this case it would be the characteristics of the remote care device, that patients would be able to trade against each other. The 5 themes adapted to directly correspond to the attributes of the DCE questionnaire design.[195] Therefore the characteristics that patients would be asked to make choices on included preferences towards 'Convenience', 'Education', 'Communication', 'Education' and 'Clinical Care'.

The number of 'levels' corresponds to the degree to which each attribute is attained, i.e. what level of attainment of a particular attribute the remote care has. For example, level 0 may mean that the remote care does not have the specified attribute, and level 1 means that it does. This allows us to create models of two remote care technologies that can be compared to each other based on different levels of each attribute.

A common option for DCE design is to have three levels for categorical attributes, a positive, negative and a neutral level. However, we opted to set only two levels: positive and negative, based on the way we characterised each patient experience during our thematic analysis. In our study we observed that experiences that were likely to fall into either a positive or negative category, where experiences that indicated there was an absence of a certain attribute (neutral) were seen as a negative experience. For example in the attribute of clinical care, the intervention may improve current practice (positive) or it may worsen it (negative).[195] In some cases, clinical care may be unaffected by the intervention, (neutral) and this is still viewed as a negative experience; therefore the attribute both being absent and being decreased are both seen as a negative experience, so neutral and negative are classed as the same level. This allows us to set a series of levels by which current and future interventions could be easily mapped against, making the outcome easier to interpret and thus use for the purpose of technology design.[196] Furthermore, these levels help define the factors of the technology and give more definition to the scenario. Since these themes were generated from grounded theory, the terminology used in the description of these may have a variety of contexts of interpretation. Therefore a clear description needed to be provided for each attribute in relation to remote care within the questionnaire itself, for the sake of the participants. A full list of these attributes and the description for each level is shown in Table 3.1.

3.2.1 Questionnaire construction

The questionnaire asked which combination of remote care technology attributes would participants prefer to have and use. This forced a choice between two alternative remote care technologies, each with different and opposing attributes, i.e. a positive

level in one attribute in choice A means that the alternative, choice B, will have the negative level of that same attribute. Each choice was therefore mutually exclusive. A forced choice was used in order to reduce the choice complexity of adding an opt-out alternative to each scenario, which minimises questionnaire fatigue. Furthermore, the aims of the study involved contrasting different attributes against each other, rather than offering an option to opt out.

The choice sets (i.e. the combination of which levels of each attribute to group together per question) were assigned based on a pre-determined, orthogonal design algorithm provided by the master list from Kocur and colleagues.[197] This was used to determine the number of questions (trials) as well as the choice sets in each trial pertaining to a discrete choice questionnaire containing 5 attributes with 2 levels each. This resulted in 16 trials, each of which contained a choice between two discrete options. The order of the questions was then randomised, in order to mask the pattern of the choice sets. The attributes were listed in alphabetical order in each question.[198, 199]

Table 3.1 Descriptions of each attribute and level in the discrete choice experiment

Attribute	Description	Level	Level Description
Communication	The ability of the technology to create increased contact and follow up between patients and others, including healthcare staff, family, carers or other patients	0	Reduces or does not improve opportunities for contact and communication
		1	The technology increases opportunities for contacts and communication
Clinical Care	The technology in some way affects the current clinical care given to the patient for their heart failure condition.	0	The technology makes no impact or even worsens current clinical care
		1	Improves clinical care from current practice, or provides more options for medical management, including providing information to make better decisions on care
Education	The impact of the technology on patients' knowledge about their health and self-care	0	There is no improvement in knowledge or ability to self-care
		1	The technology provides details that clarifies and provides useful information to the patient about their condition and aids in their self-care and management
Ease of Use	The intuitiveness and relative ease that the technology can be introduced and used by new users, including technical difficulties and jargon	0	The technology is overly complex, with little technical support and may have a high rate of technical difficulties and complications, or is difficult to access for new users
		1	The technology is easy and intuitive to use, requires relatively little support, or is easy to understand and use by a wide audience
Convenience	The measure of how much time and effort is saved by the use of the technology compared to normal care. Also relates to the level of comfort afforded by the technology in the patient's home.	0	There is no difference in the amount of time and effort required for self-care actions, or the device creates more work for the patient and requires extra time to use, or it creates increased worry or stress
		1	The device functions to save time, such as automating processes or providing relevant information at the right time, and results in less work for self-care actions, or allows the patient to be more comfortable in their own home environment

3.2.2 Patient Public Involvement

The design of the questionnaire underwent several iterations as it was reviewed by members of the research team, internal and external research staff, and finally the PERMIT patient advisory group. This advisory group is a CLAHRC-supported patient participation group who met regularly at Liverpool Heart and Chest Hospital NHS Foundation Trust (LHCH), and comprised 5 cardiac patients and a PPI facilitator who helped with the research. The patients involved are listed in the acknowledgements section of this thesis. The PERMIT patient advisory group regularly met in LHCH to discuss the research and input into its design and interpretation. The group's input included feedback on the initial design of the survey, pilot testing of the survey for comprehension and usability, and contributing to the patient information leaflet. As a result of the pilot testing within this patient group, several changes to the questionnaire design were made, including extending the introductory participant information section to provide more background for the study, and make it more readable, and also to include further information about the overall project in the information sheet. The information provided for participants about the study is laid out in Appendix 10. The group also helped design the layout of the questionnaire by testing various versions of the questions laid out in different formats. This was useful in both clarifying the understanding of the attributes for patients in the form of scenarios, and in helping make the design of the questions easy to understand, with detailed instructions. The instructions for answering the questionnaire can be found in Appendix 11, and the questionnaire itself can be found in Appendix 12.

In addition to their help with the design of the survey, several of the patients also supported the dissemination of the survey through their contacts with other patient groups (e.g. societies and charities).

3.2.3 Sample size

For calculating the sample size required, a general rule was adopted from established methods for determining minimum sample sizes for conjoint analyses. The following formula was used for this:[200]

$N > 500\ c / (t * a)$

Where (*N*) is the minimum sample size, (*c*) is the number of levels, (*t*) is the number of trials or questions and (*a*) is the number of alternative answers.

In this study, c=2 (the number of levels for the each attribute is 2), a=2 (alternatives of A or B), and t=16 main questions.

Therefore:

$N > 500 * 2 / 16 * 2 = 31.25$

For a 16-question survey with 2 choices, the recommended minimum response size for accurate analysis was rounded up to 32 participants. However, this is a general rule that approximates sample size, and as such should be considered in the context of other similar studies of this size. Other discrete choice experiments with a similar number of questions often aim for a typical sample size of around 100.[201] We therefore took 32 as a minimum, but left the online survey open until the end of the study window, to capture as many responses as we could within the study time.

3.2.4 Criteria for patient participation

The following inclusion criteria were used for survey participation:

1. Participants aged over 18 (self-reported by questionnaire)

2. Participants must have had a formal diagnosis relating to any form of chronic heart failure, which may include infective, congenital or cardiomyopathy.

The following exclusion criteria were used:

1. Participants aged 18 or under (self-reported)

2. Participants not diagnosed with chronic heart failure

3. Participants diagnosed with acute heart failure only, without any chronic component

4. Non-English speaking patients (questionnaire only available in English)

3.2.5 Recruitment

Participants were recruited online via charities and organisations associated with patients who have heart failure. These organisations were invited to help distribute the online link to the survey which could be used by any number of individual participants who wished to take part in the study. The organisations which were contacted included:

- Pumping Marvellous
- Cardiomyopathy UK
- Heart UK
- British Cardiovascular Society
- British Society of Heart Failure
- Heart failure society of America
- British Heart Foundation
- Age UK

- Age concern
- Liverpool Heart and Chest Trust Members Matters
- Closed groups on social media:
    - Heart Failure Aware
    - Heart Failure Matters!
    - Chronic Heart Failure
    - Congestive heart failure support
    - Congestive heart failure support group
    - Daily strength heart failure support group
    - Help medical research chronic heart failure group
    - Pacemaker support group
    - Young pacemaker patients and supporters
    - Pacemaker and ICD support group
    - Living with ICD support group
    - Hypertrophic cardiomyopathy association

3.2.6 Consent and ethics committee approval

In line with HRA guidance on 'Applying a proportionate approach to the process of seeking consent',[202] online surveys such as this do not need to include a consent form as long as participants are provided with sufficient information to reach an informed decision on whether to respond. The process of completing and submitting the survey is part of the consent decision making process. Therefore, while there was no formal consent form, appropriate and substantial information was provided for respondents to make an informed choice as to whether to proceed with the questionnaire or not. This information was edited and accepted by our own heart

failure patient support group and approved by the research ethics committee at the University of Liverpool (reference number 3314).

3.2.7 Participant Perspective

Participants were provided with a web link via contributing charities and organisations that directed to an online version of the questionnaire. Participants were then presented with information in lay terms explaining the purpose of the survey, the inclusion criteria and its intended aims and benefits. They were then asked to complete the short survey comprising of 16 questions. The questions were multiple-choice, in the form of a choice of two different options of remote care technology, with tick-box input for each question. In each question, they were asked to tick one of the two choices of remote care technology according to which one they preferred, from the descriptions given. No further input from the patient was requested. After the survey was complete, the webpage automatically anonymised the data. The data was then collected from the webserver and stored securely on encrypted university intranet servers.

3.2.8 Confidentiality

The survey was exported online using a secure digital platform (SurveyMonkey) which complies with EU Privacy Laws and GDPR regulations, as well as being registered under the Data Protection Act. This online platform was used to create a web link which was the primary means for distribution of the survey to participants. No personal data was collected by the research team that could identify any of the participants, nor was there any direct contact between the research staff and participants.

3.2.9 Analysis

The responses were analysed using limited dependent-variable models to determine preference weights of each attribute.[203] The preference weights provided an indication of the relative importance of each individual attribute to participants. From this we can infer which attributes participants are willing to trade in favour of others when making their choices.

This discrete choice experiment is classified as a forced-choice, five-attribute, two-level, two-alternative questionnaire. As both the choices and the levels are binary, an appropriate limited dependent variable choice model which can be used in this case is binary logit, or logistic regression.[203] Binary logit uses a logarithmic function to determine the predicted outcome of a binary variable. The logarithmic function ensures the prediction values are constrained between 0 and 1. This function can be replaced with a normal distribution by using a probit model, but the logit model outputs the preference weights as the natural log of the odds of each of the attributes, which can be more directly interpretable.[204]

The logit definition is as follows:[205]

$$\text{Logit}(P) = \log(\text{odds}) = \log(P/(1-P))$$

As part of the regression, we assign logit(P) as a linear function of any given attribute Xi, so that:

$$\log(P/(1-P)) = a + bXi = Ui$$

Where:

P = probability (of choosing this option)

a = reference value or constant

b = co-efficient of attribute X

i = attribute number

Ui = utility of the alternative

The logit value is proportional to the odds of an attribute, affecting the probability of choosing an alternative. Thus, these values can be compared directly as preference weights for each variable, and contrasted to see the extent to which patients are prepared to trade one attribute for another. The preference value for each attribute is also known as utility, or the chance of choosing the selected alternative, which is, assuming that patients act rationally to maximise their utility, equal to the importance of the attribute to patients. In order to standardise for the effect of heterogeneity of each participant, random effects were added to create a mixed binary logit model, which would be more representative of the patient cohort.[205, 206] The random intercept was necessary in order to account for non-independence of the data and to

allow for the heterogeneity between individual patients. The dataset was analysed using RStudio version 1.0.136, which is a platform for the statistical programming language R. These calculations were also corroborated using STATA/MP 13.0.

3.3 Results

The survey was open to the public between 3/6/18 – 14/10/18, a total of 133 days. A total of 94 completed responses were obtained from the online questionnaire, with a 56% non-completion rate from the online survey, so the online questionnaire was initiated by at least 164 participants. Due to the open nature of the distribution to social media it is difficult to estimate the total number of potential participants the online link was distributed to. A limited trial of the paper questionnaire was also undertaken in local heart failure community clinics, generating 1 completed response and 2 incomplete responses. Visual inspection of the data was done to identify non-differentiation, and two online responses were omitted due to flat-lining (all responses from a participant were either the A choice or the B choice). This left a total included sample of 93 responses. We identified some positive attribute dominance in the responses (where a respondent always chose the option with a positive level in a single attribute: 10 participants had positive dominance for 'clinical care', 3 for 'education', 2 for 'ease of use' and 1 for 'communication'. There were no cases of negative attribute dominance in the data. The main outputs of the mixed binary logit analysis results are displayed in Table 3.2.[207]

Each coefficient was highly statistically significant, indicating that there was a sufficient sample size and significant effect of each attribute on patient choice. The goodness of fit of this analysis was evaluated using the pseudo R-squared of the logit

model, which showed a value 0.1833. This means the attributes presented in the model can explain about 18% of the variance in choice of each participant, which is a typical result for a discrete-choice experiment of this size.[201]

We can obtain the utility value of each choice by adding the constant with the coefficients of each attribute present. This value is a log of the odds, and so we can obtain the odds by exponentiating the utility. To convert this to percentage probability, i.e. the likelihood of choosing this remote care device as opposed to the alternative, we divided the Odds by 1+Odds.[208]

Table 3.2 Coefficient values for each theme based on mixed model binary logit

Attribute	**Coefficient**	**95% Confidence Interval**		**p-value**
(Intercept)	-3.35687	-3.653542	-3.060202	<2e-16
Clinical Care	2.02168	1.810275	2.233077	<2e-16
Education	1.25251	1.077143	1.427876	<2e-16
Convenience	1.24481	1.053469	1.436149	<2e-16
Ease of Use	1.15453	0.9823047	1.326756	<2e-16
Communication	1.04022	0.8644074	1.216029	<2e-16

To summarise:

$a + bXi = Ui = \log(odds) = \log(P/(1-P))$

$Exp(Ui) = odds = P/1-P$

$P = Odds/1+odds$

Where

P = probability

a = reference value or constant

b = coefficient of attribute X

i = attribute number

Ui = utility of the alternative

The utility value was used as an analogue for the priority of choice of each alternative compared to another, the higher the utility score, the greater the chance that it was preferred by participants. This value was proportional to the calculated coefficients for each attribute, so coefficients can be compared against each other for individual attributes and utility scores can be compared for evaluating complete choice sets (different combinations of attributes). The total utility score as well as OR and percentage probabilities for each of the 32 possible combinations of present/absent attributes are shown in Table 3.3.

Table 3.3 Utility, odds, and percentage probability values for all 32 combinations of attributes

Communication	Clinical care	Education	Ease of use	Convenience	Utility	Odds	% probability
1	1	1	1	1	3.36	28.70	96.63%
0	1	1	1	1	2.32	10.14	91.02%
1	1	1	0	1	2.20	9.05	90.05%
1	1	1	1	0	2.11	8.27	89.21%
1	1	0	1	1	2.10	8.20	89.13%
1	0	1	1	1	1.34	3.80	79.17%
0	1	1	0	1	1.16	3.20	76.17%
0	1	1	1	0	1.07	2.92	74.49%
0	1	0	1	1	1.06	2.90	74.35%
1	1	1	0	0	0.96	2.61	72.26%
1	1	0	0	1	0.95	2.59	72.11%
1	1	0	1	0	0.86	2.36	70.26%
0	0	1	1	1	0.29	1.34	57.32%
1	0	1	0	1	0.18	1.20	54.50%
1	0	1	1	0	0.09	1.09	52.26%
1	0	0	1	1	0.08	1.09	52.07%
0	1	1	0	0	-0.08	0.92	47.93%
0	1	0	0	1	-0.09	0.91	47.74%
0	1	0	1	0	-0.18	0.83	45.50%
1	1	0	0	0	-0.29	0.74	42.68%
0	0	1	0	1	-0.86	0.42	29.74%
0	0	1	1	0	-0.95	0.39	27.89%
0	0	0	1	1	-0.96	0.38	27.74%
1	0	1	0	0	-1.06	0.35	25.65%
1	0	0	0	1	-1.07	0.34	25.51%
1	0	0	1	0	-1.16	0.31	23.83%
0	1	0	0	0	-1.34	0.26	20.83%
0	0	1	0	0	-2.10	0.12	10.87%
0	0	0	0	1	-2.11	0.12	10.79%
0	0	0	1	0	-2.20	0.11	9.95%
1	0	0	0	0	-2.32	0.10	8.98%
0	0	0	0	0	-3.36	0.03	3.37%

3.4 Discussion

3.4.1 Interpretation

As evident from the results, the ranking of importance of these remote care attributes was valued as follows:

1) Clinical Care
2) Education
3) Convenience
4) Ease of Use
5) Communication

Based on the coefficients alone, ‘clinical care’ was almost twice as important as the lowest scoring variable, ‘communication’, which had the preference value closest to 1. Therefore, patients are almost twice as likely to trade ‘clinical care’ over ‘communication’ when choosing a remote care intervention. In context, this means that a remote care intervention which leads to an improvement in the patient’s current medical care, is almost twice as likely to be preferred over a remote care device which does not improve clinical care, even if this device provides more opportunities to speak with a clinician or nurse. The attributes of ‘education’ and ‘convenience’ had similar preference values, which were around 20% greater than ‘communication’. ‘Ease of use’ was shown to be 11% more important than ‘communication’.

Table 3.3 shows data for all the potential permutations of attributes that would be possible in a single remote care intervention. The utility is a measure of patient preference for the particular combination of attributes. The percentage probability column shows the likelihood in percentage terms of a patient choosing this combination of attributes in a remote care intervention versus a remote care

intervention with a utility of zero. As such, this can also be used as a marker of preference.

This table is most useful for comparing differences in preferences between two different remote care technologies. Since the coefficients are symmetrical around 0, the closer a utility value is to 0, the closer the preference probability is to 50%. Therefore, to achieve a preference probability over 50% (i.e. more likely to prefer a remote care device over one that has utility of 0), it is clear that a remote care intervention needs to offer at least 3 of the factors of 'communication', 'convenience', 'ease of use' or 'education', or alternately, offer 1 of these factors in addition to 'clinical care'. This confirms and validates the postulation that 'clinical care' can be practically traded for two other remote care factors in the preference of patients.

3.4.2 How to use the data for comparative analysis

3.4.2.1 *Comparing existing technologies*

For designers looking to compare two different types of intervention, e.g. with and without a certain attribute included, table 3.3 can be used to calculate the 'marginal probability' or the percentage difference in preference of one intervention over another. This can be done by choosing the row which most corresponds to each individual remote care device, and then subtracting the percentage probabilities from each other to get the difference in probability.

For example, in a remote care intervention with no attributes present (0/0/0/0/0), the percentage probability of choosing this device compared to one with 0 utility is 3.37%. The marginal probability gained by adding the attribute of 'communication' to this

intervention (1/0/0/0/0) is 8.98 – 3.37 = +5.61%. However, the marginal probability of adding 'clinical care' instead (0/1/0/0/0) is 20.83 – 3.37 = +17.46%

As the example shows, 'clinical care' has a much greater impact on patient preference than 'communication', and should thus be prioritised when making additions to the existing remote care technology. Other remote care devices can be compared in this way against versions of similar devices or when determining which attribute to focus on improving, given a limited amount of resources.

3.4.2.2 *Improving a remote care technology: adding attributes*

We can use the above formula to obtain the mean increase in preference percentage of adding each attribute, by calculating the marginal probability of adding the attribute to each permutation which excludes it, and averaging out the values. Doing this gives us the following mean marginal probabilities per attribute: 'communication' = +18.04%, 'ease of use'= +20.1%, 'convenience' = +21.76%, 'education' = +21.9%, and 'clinical care' = +37.55%. These values could also be interpreted as the relative increase in patient preference gained by adding this attribute to an intervention that lacks it. These values can be used to directly inform the design of new technology in order to increase engagement with this patient group.

3.4.3 Limitations

Limitations of the study can be divided into those inherent to the methodology, and those related to the questionnaire design.

3.4.3.1 Methodological limitations

Assuming that participants are rational

With any conjoint analysis using fixed effects, the statistical model assigned to regress the choices will assume that each participant is a rational entity. In other words, they will always choose the option which maximises their utility. This assumption is not always correct, and can lead to bias. In our study we tried to mitigate this bias by adding a random effect to model heterogeneity of preference choices, even if they might be irrational (or of less utility). Even then, this bias cannot be mitigated completely. Therefore, while the analysis results are significant they do not necessarily apply equally to each patient's individual preference.[209]

Assuming that calculated utility is an analogue for patient preference

As mentioned previously, human participants do not always make choices in a rational manner. Therefore, even if the calculated utility of an intervention is higher than the alternatives, the patient will not always prefer this intervention. We move from this logical pathway into the assumption that designing with these specific attributes in mind will equate to a high preference rating for patients. This assumption does not consider other factors which were not tested and may have more of an influencing effect on patient choice. Therefore, this study can only surmise on the effects of the recorded attributes in relation to one another, and relies on the foundation of its supporting research to substantiate the list of included attributes that were tested.[193]

Assuming participants are attentive

The methodology of the questionnaire and subsequent analysis takes each question as its own individual experiment, without accounting for the accumulated fatigue on the participant after subsequent questions. This therefore assumes that the participant is equally attentive on question 1 as they are on question 13, and this may not be the case.[210]

Lack of a 'cost' measure as an attribute

As the attributes were generated from qualitative work, the factor of 'cost' which is normally assessed in this manner by means of adding an attribute which asks how much the participant is willing to pay for certain factors, is missing. The remote care intervention that participants were asked to envision was theoretical, and therefore there is no real-world cost to incorporate in the assessment. Furthermore, the aims of the study focus on the priority of these thematic attributes to the design of the device for patient preference. This means that the monetary value participants are willing to trade for attributes cannot be directly derived from this data. However, it is worthwhile considering that cost implications played a role in defining the attribute of 'ease of use' in the original thematic synthesis, as high cost and maintenance requirements of the device contributed to poor accessibility of the intervention and was seen to impact the ease of use for patients.[211]

Theoretical remote care device

In many DCEs, the alternative choices are based on existing interventions or ones which are ready to market to the user base. In this study, the alternatives in each choice

set ask the participant to imagine a theoretical remote care device. While this means that the results are not directly applicable to any one existing remote care technology, the hope is that the breadth of the question is adaptable, and therefore the output of the data can have an impact on a wide variety of technology designs in the future. Nevertheless, this theoretical situation that the participants are placed in makes them vulnerable to hypothetical bias which can lead to a discrepancy between their stated preference and the actual preference when it comes to choosing a device in their lives.[212]

Preconceived bias

Patients may have entered the study with a previous knowledge or experience with a specific remote care technology, which influenced their questionnaire responses, rather than taking an objective approach, and this may be reflected in the responses to certain attributes. In many ways however, this perception bias will continue to exist within this specific user base, and capturing opinions despite this, is still of value since a mitigating effect would be to target a population as homogenous as possible in their medical background.[213]

Selection Bias

Since this was mainly an online survey distributed across social media groups, it stands to reason that the main responders may consist of a select group of heart failure patients who are keenly engaged with the internet, technology and social media, and are thus more inclined towards new technological advancements such as remote care. This study acknowledges the fact that there is a large untapped cohort of participants, who

may be elderly and not keen to interact with technology that have been missed in this report by virtue of its distribution methods. Although we attempted to collect questionnaires on paper via local community heart failure nurses, the poor response was indicative that this cohort would be difficult to engage with and obtain responses from. This means that the results of this study should be interpreted within the context of patients who are generally keen supporters of new technology and opinions from other sources may contrast those that have been shown here.[214]

3.4.3.2 Questionnaire design limitations

Lack of 'neutral' level

When designing the questionnaire, there was a lack of a third 'neutral' level for each attribute: either the attribute was present in the remote care technology, or it was not. This means that there was no 'neither' option for the participant to choose, to indicate that a specific attribute was unimportant in their decision-making. Furthermore, the negative level was often used to effectively indicate two different levels by specifying both an 'absence' and 'negative' effect of the attribute within the meaning. Although we chose to omit the neutral level from the questionnaire design, the benefit of this is that it allows the analysis to be more straightforward in terms of the binary logit analysis rather than adopting a multinomial logit model which requires more assumptions.[215] Another benefit to the two level system was that the choice burden on the participants was minimised which likely improved completion rates. Furthermore, additional choice sets would have been required to obtain the same effect, as well as a larger sample size to power the analysis. Within the constraints of this study and our aim to assess the relative value of the 5 themes, the two-level design was the most appropriate one.

Questionnaire length

In designing the questionnaire, there was an option of creating either an 8-question design or a 16-question design. We opted for the latter in order to obtain a greater statistical effect from each respondent, though perhaps in hindsight this may have led to the large percentage of non-completers. Future questionnaire designers should consider that reducing the number of questions, while limiting the range of the alternatives presented, could lead to a greater completion rate.[210]

No participant information collected

No personal data was collected from the questionnaire, and therefore no characteristics of the individuals were available in the data to input into the choice model as random effects. Furthermore, since we do not have basic demographic information, we are unable to determine the general context of the population included within this study, except that each participant has self-admitted to suffering from heart failure. More detailed information regarding patient diagnoses, their age, and whether they had used remote care technologies in the past may have allowed us to mitigate some of our earlier stated biases within the questionnaire and review the results in a clearer context within the target population. For example, it would have clarified whether the age range of participants matched the mean for heart failure diagnosis, or indicated if respondents from marginalised groups were represented. While this information would have been helpful, the results we obtained showed a significant level of effect regardless. In addition, reducing the amount of personal information requested allowed us to distribute the survey more easily in a widespread manner.

Low number of attributes

The attributes were generated from a thematic synthesis process which created 5 themes. As these themes were broad in order to encapsulate the range of user experience, the result of having relatively few themes means that there may be many other factors which may specifically explain the choices better that were not included in the attributes. However, it is difficult to include every factor that would go into the choices made by patients without encumbering the questionnaire, and so we felt that these relatively few themes and levels were a good compromise for the methodology and allowed the questionnaire to be manageable, whilst including the broad scale of relevant experiences.[215]

3.4.4 Conclusion

This study has gathered opinions from a cohort of 93 patients with heart failure regarding their technology preferences in remote care. The analysis resulted in a significant effect, able to rank the identified attributes in terms of importance in order to highlight which has more value to patient users. Based on these findings, future remote care technology design should prioritise clinical care improvements first and foremost. Patient education and convenience are secondary, while ease of use is also significant though to a lesser extent. Finally, communication is preferred least, but still contributed a substantial effect. Therefore, if ever a trade-off is required, communication, ease of use, convenience or education may be sacrificed for the sake of providing effective clinical care, and still provide enough incentive for patient preference to promote engagement. While these findings are clear from the data, it is

important that they be regarded in the context of this patient cohort of heart failure patients that are able to engage with online media.

Using this data, we have demonstrated an intuitive and simple way to predict level of engagement and preference of patients based on the attributes of a remote care technology. It is envisioned that technology companies and designers can use these findings as a useful way to check the effectiveness of a device's features in engaging the patient user-base. Further, it can help develop a working plan of improvement for devices based on the attributes desired. While this study focuses on patient preference, it will be up to the third party to determine other practical aspects of technology refinement such as cost, administration, and resources, to judge whether the change is worthwhile. However, by taking the first steps to quantify the level of engagement gained from each change, we hope to make this decision easier for those that seek to bring remote care technology to these patients in an effective and engaging manner, to reduce the burden of morbidity from heart failure.

CHAPTER 4

DETERMINING CLINICAL ASSOCIATIONS WITH RENAL FUNCTION OVER TIME

CHAPTER 4: DETERMINING CLINICAL ASSOCIATIONS WITH RENAL FUNCTION OVER TIME

4.1 Introduction

The purpose of the PERMIT project is to reduce the rates of renal decline over time in patients with chronic heart failure in the community, by facilitating a pathway of generating clinical guidance using predictive analysis. As discussed in Chapter 1, guidelines regarding renal function monitoring in these patients are sparse, based on anecdotal evidence, and unable to adapt to individual circumstances. A more personalised guideline could lead to earlier clinical intervention in patients who are at increased risk of renal decline, before their disease progresses to a level requiring hospital care, thus potentially reducing mortality and morbidity rates in these patients. This has led us to try a machine-learning approach for predicting renal decline; a characteristic advantage of this approach is the ability to process large amounts of data and output unique predictions based on an individual's clinical information, personalising medical management.

The future goal of the PERMIT project is to create a foundation for producing flexible clinical guidelines that can tailor the frequency of renal monitoring on a case-by-case basis for heart failure patients. To this end, the immediate aim of this project was to create a predictive model for renal function decline over time, in order to be the basis for which future monitoring could be personalised.

In order to create this predictive algorithm, access to a large primary care clinical dataset was obtained, and longitudinal patient information was extracted. Clinical variables which were relevant to renal decline were identified, and assessed for potential inclusion within the predictive algorithm. This chapter focuses on this process, beginning with obtaining the large datasets, cleaning and pre-processing the raw data into a usable format, and then determining the appropriate variables for predicting renal function over time. The results of this analysis will also have intrinsic

value in describing this cohort of heart failure patients in detail, and suggesting which variables could be used by clinicians in order to assess renal severity and risk. Chapter 5 will then discuss the machine-learning strategies employed in depth, and the process that was used to obtain the current predictive algorithm, using the data from this analysis.

4.2 Methods

4.2.1 Database requisites

For a database to accurately simulate renal function over time it must meet specific requirements for analysis, especially in the context of machine-learning methodology. These requirements are as follows:

- A comprehensive list of clinical variables

In order to determine which variables are most important for predicting renal function, we did not start with a pre-determined set of clinical variables a priori. Instead, we extracted all possible clinical information available regarding each patient over time, categorised these as distinct variables, and used a data-driven approach to identify which ones are most strongly linked to renal function trends.

- Longitudinal data from primary care

In order to create a predictive algorithm for estimating renal function at certain time points, as well as determining which variables have an effect on renal function over time, longitudinal analysis of patient data was required. In order to maximise the input

data, a large number of time points for each patient is required. Primary care data, which involves many years of follow up per patient throughout their lives, was best suited for this case.

- A clinical output as an analogue for renal function

In order for a prediction to occur, an output variable must be set which emulates renal function and can be tracked over time. The frequency of testing of this variable can then act as the fixed time point from which prediction could take place. Identifying the most appropriate variable is a key step in the analysis

- Data is able to be split into different sets

Within machine learning methodology, once an algorithm is created it must be tested within the same dataset to ensure it can adapt to new data correctly (internal validation). Therefore the final dataset will need to be split into a 'training dataset' where the main analysis will take place, and a 'testing dataset' which will be effectively hidden from all analysis steps until the final stage of validation.

- The data format is uniform and usable by multiple platforms

While the majority of the analysis uses R as its statistical programming platform, having a format that is usable by multiple statistical packages allows the use of methodologies which are exclusive to different platforms, as some machine learning methods are. Keeping a uniform format allows us to expand the range of analysis for this and future uses.

4.2.2 Summary of methodology

In order to create this dataset and complete the subsequent correlation study, the following steps were taken in this order:

1. **Identifying variables of interest** – Work was done to determine which clinical variables existed within the data that were relevant to the study's aims and could be extracted
2. **Determining an output variable for renal function over time** – Variables which could potentially be analogues for renal function over time were evaluated for appropriateness for the prediction output.
3. **Defining the study population** – To maximise the accuracy of the prediction, we aimed to create a cohesive dataset of patients with the same clinical profile centred around heart failure.
4. **Data acquisition** – Data was applied for from clinical primary care databases both locally and nationally.
5. **Extracting variables of interest** – Raw data was then compiled and sorted into these variables, using the associated read codes appropriate for each database.
6. **Mapping out renal function over time longitudinally** – Once the output variable representing renal function was decided, the rest of the clinical covariates were aligned to the timeline of this output, to emulate the change in clinical variables with the renal function trend over time.
7. **Pre-processing of dataset** – Steps were taken to ensure the validity of the data for each variable, such as defining acceptable value ranges, and creating assumptions for drug prescribing.

8. **Addressing missingness** – Once the pre-processing was complete, the variables could be examined in further detail, and those that were found to have significant levels of missing data were filtered out.
9. **Imputation** – To facilitate both regression studies and machine learning methodologies, the remaining clinical variables which contained missing data underwent Random Forest imputation[216] to create a complete dataset. This allowed all existing data to be accounted for without excluding any time points due to missingness.
10. **Splitting datasets** – As discussed previously, the validation step for machine learning methodologies required a 'hidden' set of data, which was randomly selected and partitioned off from the main dataset at this stage of the study.
11. **Variable correlation study** – We used linear mixed model regression for each clinical variable, to determine the importance of each variable to predicting renal function over time. This led to a series of p-values that signify how strongly associated each variable was to renal function for this patient cohort. These values could be compared and assessed to determine which variables to enter into the predictive algorithm.

Each of these steps will be discussed in further detail.

4.2.3 Identifying variables of interest

In order to ascertain the clinical variables which would make the most impact on the end point analysis of determining renal function over time, a combination of literature searches as well as clinical knowledge was used. This created a comprehensive list of included covariates that provided richness of data for the proceeding analysis steps.

Pre-requisites for relevant covariates included:

a) Being readily accessible in primary care databases, and;
b) In some way either altered by, or were observed to have an effect on, either heart failure or renal function over time.

Described below is each variable of interest and its relevance to renal function within heart failure patients.

- **Age** – Associated with worsening renal function along with the presence of other co-morbidities which affect renal function such as hypertension.[217-219]
- **Gender** – Gender differences occur regarding the presence of certain co-morbidities that lead to renal decline such as ischaemic heart disease.[218-220]
- **Lower Super Output Area (LSOA) / Indices of multiple deprivation (IMD)** – Markers of socio-economic status. Low status is associated with both higher rates of heart failure and a greater risk of morbidity and mortality associated with this.[221, 222]
- **Ethnicity** – Racial variations exist in the way that renal function is calculated in certain populations such as in Afro-Caribbean's where the normal range of creatinine, a renal marker, is passively increased.[220]
- **Systolic (SBP), diastolic (DBP), pulse pressure (PP) and hypertension (HTN)** – BP has a direct effect on renal function. Low BP causes reduced renal perfusion, which in turn stimulates arteriolar constriction, activating compensatory mechanisms. This homeostatic mechanism is altered in heart

failure. Hypertension also leads to other co-morbidities such as ischaemic heart disease which may also cause renal decline.[223, 224]

- **Heart rate (HR)** – Increases with reduced blood pressure, which can be a sign of shock or dehydration, both of which herald a drop in renal perfusion, and can cause the activation of compensatory mechanisms.[225]
- **Diabetes Mellitus** – Diabetic nephropathy is one of the most common causes for CKD, and poorly controlled blood glucose can lead to episodes of AKI (due to dehydration and other factors), as well as a chronic decline in renal function over time.[219, 226]
- **Smoking** – Contributes to hypertension and ischaemic heart disease which have secondary effects on renal function and increase the risk of heart failure. [227, 228]
- **Body Mass Index (BMI)** – Contributes to hypertension and ischaemic heart disease risk as well as risk of diabetes. It can also have direct effects on renal dysfunction.[218, 229]
- **Atrial Fibrillation (AF)** – May be caused by left atrial dilatation, which is common in heart failure patients. The reduced efficiency of the heart also increases the risk of heart failure and can reduce renal perfusion.[230-232]
- **Ischaemic heart disease (IHD)** – An extremely common cause of heart failure that can also lead to progression of cardio-renal syndrome.[217, 224, 233]
- **Brain Natriuretic Peptide (BNP) and End-Terminal Pro-Brain Natriuretic Peptide (NTproBNP)** – These hormones promote natriuresis from the body i.e. the excretion of sodium, and are excreted in response to high blood pressure. They are used as a screening tool for heart failure, and the

levels of circulating hormone are associated with severity of left ventricular dysfunction.[234]

- **Serum Creatinine** – A waste product from degrading muscle and other proteins in the body. It is effectively cleared from the body in a patient with normal renal function, and thus the level of creatinine in the blood rises in proportion to renal decline. As such, it is the foremost marker for acute renal dysfunction used in secondary care.[82]
- **Estimated Glomerular Filtration Rate (eGFR)** – This is a calculated value which is associated with renal function that considers the patient's age, gender and ethnicity as well as just their creatinine value. It is therefore the main biochemical marker for diagnosing chronic kidney disease. [235]
- **Chronic kidney disease stage (CKD)** – Clinical categories defined as stages, related to the value of a patient's eGFR, graded according to the severity of chronic renal decline.[93]
- **Serum Albumin** – Can be used as a marker of overall nutritional status, however it is also used as a comparator when measuring the level of albumin in the urine.[236]
- **Urine Albumin** – Correlates to the level of protein in the urine, also known as proteinuria or albuminuria. A high value indicates a more porous glomerular membrane which is a sign of renal damage.[237]
- **Urinary Albumin:Creatinine Ratio (ACR)** – The level of albumin protein in the urine, relative to the creatinine being excreted, which gives a more accurate representation of the level of renal damage. This variable is used as a marker for diagnosing stages of chronic kidney disease.[237, 238]

- **Haemoglobin (Hb) and gender-specific anaemia** – Anaemia is associated with high output cardiac failure, due to reduced oxygen carrying capacity in the blood. It can also occur as a result of renal failure due to the loss of production of erythropoietin (EPO) from the kidneys.[239]
- **Mean Corpuscular Volume (MCV)** – Used to assess for the cause of anaemia, it indicates the size of the red blood cells. Typically a smaller value is associated with iron deficiency, and a larger value is associated with B12 or folate deficiency as the most common causes.[240]
- **Dialysis or renal replacement therapy (RRT)** – Patients that require RRT are often in end-stage renal failure. By this point, serum monitoring of creatinine for renal function is no longer useful, as it fluctuates in line with dialysis cycles. In these patients therefore, a predictive algorithm would not be of use and so this was an important exclusion criteria for the study.[241]
- **Peripheral vascular disease (PVD)** – Associated with cardiac co-morbidities and also related to the status of renal vasculature. Patients with PVD may have reduced arterial supply to the renal system and be at higher risk of CKD. Conversely, the appearance of CKD is a risk factor for PVD.[242]
- **Acute kidney injury (AKI)** – A measure of the number of times the patient has experienced an episode of AKI, defined by KDIGO as an increase in serum creatinine more than 50% from baseline over 7 days.[243]
- **Worsening renal function class (WRF)** – A risk marker similar to AKI, triggering on episodes of creatinine rise over 6 months instead of 7 days. It is also associated with worse heart failure outcomes. A more detailed definition can be found in Chapter 1 (Table 1.1).[56]

- **Nephrectomy** – Identifying patients with nephrectomies is important to determine how the trend in renal function differs with only one functioning kidney.[244]
- **Renal malignancy** – An important consideration for patients with renal decline, and these patients may go on to have a nephrectomy.[244]
- **Renal Transplant** – Patients who required a renal transplant may have been in end-stage renal failure previously, requiring RRT. These patients would also subsequently be on immunosuppressive therapy, which can have renal sequelae. Furthermore, they would be in a higher risk category for heart failure as a result of end stage renal disease.[245, 246]
- **Serum potassium** – Potassium levels increase in chronic kidney disease due to the reduced ability to excrete potassium and maintain homeostasis once nephron function declines. Additionally, patients with CKD or hypertension may be on medications such as ACEi that increase serum potassium levels. Finally serum potassium is associated with arrhythmias which is a risk factor for chronic heart failure.[247-249]
- **Serum sodium** – Homeostasis of serum sodium is one of the vital mechanisms for controlling blood pressure. High or low sodium can also be correlated to dehydration which is a risk factor for AKI.[250, 251]
- **Uric acid** – High uric acid is associated with gout and tumour lysis syndrome, both of which have an impact on renal decline. Conversely, CKD can increase the risk of gout due to lack of ability to excrete uric acid.[252, 253]
- **Blood urea nitrogen (BUN)** – This is also known as serum urea, and it denotes further breakdown products in the blood stream that are usually filtered out by the kidneys. Much like creatinine, these are excreted in proportion to the

function of the kidney, and are thus used as a marker for renal decline. High urea is also correlated with dehydration which is a renal risk factor.[83]

- **Chronic liver disease (CLD)** – Cirrhosis and liver disease is associated with heart failure due to chronic portal hypertension, leading to venous back-pressure. It can also cause fluid retention and ascites which are exacerbated by heart and renal failure.[220, 254]
- **Immunosuppressants** – This category relates to medications that have a detrimental impact on kidney function which are taken for the purpose of immunosuppression. This indicates the patient will require these medications often long-term for either chronic inflammatory conditions or transplants, and may be a risk factor for future renal decline.[255, 256]
- **Non-steroidal anti-inflammatory drugs (NSAIDs)** – NSAIDs such as ibuprofen are analgesics that can cause acute renal decline, and if used over a long term are a risk factor for chronic kidney disease.[257]
- **Loop diuretics** – As elaborated on in Chapter 1, loop diuretics can lead to both chronic and acute kidney failure, and cause rapid dehydration if given in large doses. [258]
- **Thiazide diuretics** – As with loop diuretics, the filtering of fluid via the kidneys reduces circulating volume and thus perfusion pressure, causing acute renal decline. [60]
- **Aldosterone antagonists or mineralocorticoid receptor antagonists (MRAs)** – These medications are part of the management of heart failure. They are also known as potassium sparing diuretics, and as such, can increase potassium while also causing dehydration and associated renal consequences.[259]

- **Angiotensin converting enzyme inhibitors (ACEi)** – These medications are used both for blood pressure control and also for heart failure treatment. However, on initiation they cause a transient rise in creatinine over the short term.[73, 248, 249]
- **Angiotensin receptor blockers (ARBs)** – Used as an alternative to ACEi, if the patient is intolerant to them. They fulfil the same role, disrupting the renin-angiotensin aldosterone system (RAAS), which can lead to reduced renal perfusion. [248, 249]
- **Other nephrotoxins** – This category is for medications that do not fall into the other listed variables, but are known to cause renal impairment.

4.2.3.1 Pre-existing predictive models

We surveyed many similar existing statistical predictive models regarding renal function over time that also involved, but were not limited to, heart failure patients. These provided insights into which selected variables had the greatest potential for creating an accurate predictive model. Using a review of previous predictive models for renal function by Echouffo-Tcheugui and colleagues,[260] the most accurate models were summarised in Table 4.1 and the variables used in each model were noted for reference. This demonstrated that the common themes between the most successful models included a measure of demographics along with key co-morbidities such as hypertension, diabetes and ischaemic heart disease. Of note, the highest AUC model also included the covariate of heart failure for determining renal decline.

Table 4.1 The highest AUC value prediction models for chronic kidney disease and its progression, as published by Echouffo-Tcheugui and colleagues[260]

Paper	Variables	AUC
Bang et al 2007, 2008,2009 SCORED score**[261-263]**	Age, gender, anaemia, HTN, DMT2, CVD, CHF, PVD	0.88
Kwon et al 2012, Korean risk score**[264]**	Age, gender, anaemia, HTN, DMT2, CVD, proteinuria	0.83-0.87
Jardine et al 2012 ADVANCE Major final model**[265]**	Gender, eGFR, ACR, SBP, HbA1c, diabetic retinopathy, education completion age	0.87
Jardine et al 2012 ADVANCE Major eGFR + ACR model**[265]**	eGFR, ACR	0.82
Hippisley-Cox and Coupland 2010 QKidney score**[266]**	Age, ethnicity, deprivation, smoking, BMI, diabetes, RA, CVD, treated HTN, CHF, PVD, NSAID, FHx kidney disease, SLE, nephrolithiasis	0.88
Fox et al 2010 Framingham score 2**[267]**	Age, gender, SBP, HTN, HTN medication, smoking, BMI, HDL, diabetes, eGFR	0.81
Fox et al 2010 Framingham score 3**[267]**	Age, gender, SBP, HTN, HTN medication, smoking, BMI, HDL, diabetes, eGFR, aldosterone, homocysteine	0.82
Halbesma et al 2011 PREVEND score**[268]**	Age, urinary albumin, SBP, CRP, HTN, eGFR	0.84
Ando et al 2011 Japan/HIV score**[269]**	Age, CD4 count, diabetes, proteinuria, eGFR	0.84
O'Seaghdha et al 2012 Framingham score 4c**[270]**	Age, HTN, diabetes, eGFR, albuminuria	0.81
Alssema et al 2012, Rotterdam Hoorn score**[271]**	Age, BMI, waist circumference, HTN tx, smoking, Fhx CVD<65, Fhx DMT2	0.82

4.2.4 Determining an output variable for renal function over time

Measuring renal function in a consistent manner was essential for the predictive value of the algorithm. Identifying a variable that was present in primary care datasets that could be used as an analogue for renal decline was therefore important in order to select the machine learning process that would be used.

The qualities required of this outcome variable were as follows:

- Readily accessible in primary care datasets.
- Strongly associated with fluctuations in renal function.
- Clear and understandable to physicians to facilitate management decisions
- Recorded frequently and at multiple time points in order to lead to time point prediction and algorithm training.

Two variables met these criteria:

a) Serum creatinine

b) eGFR

Both of these variables closely relate to renal function and in addition they change dynamically based on the clinical status of the patient and renal related covariates.

There are two prevalent equations for calculating eGFR, namely the MDRD formula and the CKD-EPI formula.

i. **MDRD:**[272]

eGFR = 175 x (SCr)-1.154 x (age)-0.203 x 0.742 [if female] x 1.212 [if Black]

ii. **CKD-EPI:**[273]

eGFR = 141 x min(SCr/κ, 1)α x max(SCr /κ, 1)-1.209 x 0.993(Age) x 1.018 [if female] x 1.159 [if Black]

Where:

eGFR (estimated glomerular filtration rate) = mL/min/1.73 m^2

SCr (standardized serum creatinine) = mg/dL

κ = 0.7 (females) or 0.9 (males)

α = -0.329 (females) or -0.411 (males)

min = indicates the minimum of SCr/κ or 1

max = indicates the maximum of SCr/κ or 1

age = years

Historically, primary care practices and hospital values for eGFR were calculated using MDRD. However, the newer CKD-EPI criteria has been shown to have greater prognostic accuracy in patients with reduced renal function, and is thus being recommended for use by KDIGO guidelines, which has led to a recent shift towards this criteria.[274] Since our study uses retrospective data which crosses the boundary

of this shift, we opted to calculate both values manually using the raw data rather than take any pre-existing non-standardised calculations.

In relation to eGFR as an output variable, since we are already defining age, gender and ethnicity as covariates, creating a classification algorithm for a calculation that uses these factors may hinder the training process. In other words, having age as both an input and part of the output (as part of eGFR) would alter the predictive learning process since age is no longer an independent factor in the study. In principle, this would lead to bias and conflicts using both machine learning and statistical regression methodologies. In addition, using eGFR as an output relies on accurate retrospective ethnicity data, which was not guaranteed in this dataset. We therefore leant towards using creatinine as an output for renal function.

4.2.4.1 Renal function outcome: Log(creatinine)

Creatinine in and of itself is correlated strongly to renal function at any one point. However, the actual value can differ depending on the patient's muscle mass and ethnicity, as well as age (hence the need for the eGFR calculation). Therefore, when monitoring creatinine, it is more important to observe the individual trend over time for each patient, so it can be said that the overall trajectory of creatinine is more prognostic than the actual value.

Furthermore, the increase in creatinine over time for patients with renal injury is often non-linear. This is reflected in the KDIGO definition for acute kidney injury which is >50% increase in creatinine from a patient's baseline. This respects the fact that for patients with underlying renal disease, and a high baseline creatinine, both the daily variability and the extent to which creatinine rises is increased compared to healthy

patients. This suggests an exponential pattern wherein a high baseline creatinine leads to an even greater increase in raw creatinine at the same stage of AKI.

In order to compensate for this non-linear relationship and to make comparisons and regression models easier to compare, the logarithm of the creatinine value was used as the final output variable. Since log(creatinine) was normally distributed, it facilitated the use of statistical analyses that required this assumption. Furthermore, using a derivation of creatinine means that it can be transformed into raw creatinine or even eGFR at the output end of the algorithm as required.

4.2.5 Data acquisition

In order to provide the most information for the purpose of predicting renal function over time, a rich longitudinal dataset was sought that could provide several years' worth of clinical follow up for each patient.

Initially, the following datasets were considered:

- RCGPD
- CPRD
- SIR – Salford Integrated Records
- Q research database
- LCCG – Liverpool Clinical Commissioning Group
- ResearchOne
- HICD – Health Informatics Centre Dundee
- SAIL

Overall, the most robust and applicable dataset which suited the aims of the study within the timeframe was Salford Integrated Records (SIR), and this was used for all further analysis and prediction methods during this project.

4.2.5.1 SIR Description

Salford Integrated Records is a shared care initiative started by the Salford CCG in 2009 aimed to unify the data of the population of Salford. It consists of a clinical database which extracts information from primary and secondary healthcare services in the Salford area of Greater Manchester, UK. This dataset covers all primary care patients within the Salford area, which has a population of approximately 275,000 people at any one time. It contains retrospective data spanning as far back as 1990, however its most robust data collection practices occur after 2008. Before 2008, patients who had died were withdrawn from the dataset, and therefore the reliability of the data decreases pre-2008. Therefore the study will focus on a cohort of post-2008 patients, whose demographics and population statistics may show historic differences from current figures, and should therefore be considered in the context of this study's cohort and timeline.

Most of the data is stored as 'clinical events' which are events noted whenever a test is performed or a patient comes into clinic. Each data point has an associated 'read code' relating to the type of information stored. Read codes are the language used to catalogue the type of clinical information stored, so a specific read code may exist for 'haemoglobin' as a blood test, and this code will be time stamped and will provide the associated test value for the test within that clinical event. However, there may be several read codes for the same test and several clinical events recorded under one

associated read code but not another – the process of extracting this information is discussed later in this chapter.

Patients are free to opt-out of sharing their information with SIR at any time. In addition, there are several sensitive read codes which are not extracted from GP systems and are thus not stored within SIR, which mainly relate to HIV status.

4.2.5.2 Advantages of SIR over other datasets

SIR contains medication prescription data dispensed from primary care. It also contains a system which incorporates hospital investigations with GP information, and so it could be said to have second degree linkage with hospital data, providing a more complete picture of each patient's journey. This is especially useful for longitudinal case analyses such as this.

4.2.5.3 Drawbacks of SIR over other datasets

Within the Salford area, there are relatively few ethnic minority patients, with over 95% being classed as 'White British' within the dataset obtained, which would need to be considered in any analytical output emerging from using its dataset. Localised within one area, it could also be said that the size of the population is relatively small compared to other national datasets. Conversely, this made the data a useful test-bed to trial different methods of machine learning with a higher turnover than larger sets of data.

4.2.6 Defining the study population

4.2.6.1 Study window

While the raw data was retrospective up to 1990, mortality data in SIR was missing before 2008. In order to mitigate the bias formed from the exclusion of mortality data, it was decided that patients would enter the study no earlier than January 2008. The application for data was requested in August 2016. Therefore the study window ranged from 01/01/2008 – 01/08/2016. All patients were followed-up from the index date to either the last date of data collection, the date of transfer of the patient out of the catchment area, the date of the patient's death, or the end of the study (01/08/2016), whichever happened first.

4.2.6.2 Inclusion criteria for patients

Patients entered the database if the following conditions were met:

- They were newly diagnosed with chronic heart failure after 01/01/2008
- Their age was 18 or over at the point of heart failure diagnosis
- They were registered with a GP for 2 or more years after 01/01/2008
- The patient had 2 or more creatinine tests after their heart failure diagnosis date (post-2008)

These criteria ensured that we had a homogenous sample of adult chronic heart failure patients, all within the same early stage of heart failure diagnosis, which would reduce the bias during the predictive stage of the analysis.

4.2.6.3 Exclusion criteria for patients

Patients were excluded from the database despite meeting the inclusion criteria:

a) At the point at which they required renal replacement therapy. This is because once renal replacement therapy is initiated, large fluctuations in creatinine would occur in the patient's trend data, which would be iatrogenic, and would therefore disrupt the predictive analysis during the learning stage.

b) All renal function data before the index date of heart failure diagnosis was excluded. This was so that the predictive algorithm could be focused on the target population of patients who were diagnosed with heart failure. Therefore, including patients before their diagnosis would skew the cohort and lead to a bias in the data.

4.2.7 Extracting variables of interest

All clinical data except for demographics were coded as 'read codes'. In this study, the main coding language was 'Read code 5-byte version 2'.

The inclusion and exclusion criteria were applied to the raw data obtained from SIR from within our allotted study window. To identify patients diagnosed with heart failure in the dataset, we looked for the read codes most associated with chronic heart failure. The index point of diagnosis was the date the first event occurred in the patient data. Appendix 13 outlines the read codes used to identify cases of heart failure from patient information. By selecting patient data between 01/01/2008 and 01/08/2016, we obtained our cohort of heart failure patients. This was further filtered by excluding patients diagnosed with heart failure below the age of 18. Furthermore, patients were only included if their index date of heart failure diagnosis fell within the study window.

Having obtained the heart failure cohort, we then extracted each clinical variable using their associated read codes. The list of the specific codes used for all variables can be found in Appendix 14. The code lists used were derived by manually inspecting the read code version 2 clinical events listings and searching for the appropriate parameters matching the clinical variable. Then our primary lists were cross-referenced with several published online clinical lists for variables (which are available at ClinicalCodes.org)[275].

Demographic information for each patient, including LSOA and ethnicity, were provided in a separate dataset and were linked by Patient ID to the remaining data.

Some clinical variables that included formulas such as eGFR and BMI required processing after data extraction. Each of these, with the formulas used are listed in Appendix 15. All processing of the data was carried out in R software,

4.2.8 Mapping out renal function over time longitudinally

In order to make sense of the data longitudinally, a standardised timeline by which to map the variables for each patient was required. Since the output variable was log(creatinine), effects that would alter creatinine over time were the main focus of the longitudinal analysis. Thus, ‘creatinine blood test events’ was set as the standard by which the timing of the other covariates would be mapped against. In other words, each discrete time point for a patient would equal the exact number of times creatinine level was tested in the included data for that patient. The other clinical covariates would then be ‘mapped’ to that time point, by taking the last clinical value of each variable that occurred previous to that time point. This allowed us to see the whole

clinical status of a patient at any time renal function was measured, which led us to correlate changes in the covariates with each change in creatinine over time.

For the purpose of future prediction, we used the closest clinical values in time which occurred previous to each creatinine test taken, as opposed to the overall closest clinical value (from before and after the creatinine test was taken). This ensures that the algorithm generated will use retrospective information only to make predictions, as future clinical values would not be available at the point of use.

4.2.9 Pre-processing of the dataset

The following processes were used on the longitudinally-aligned raw data to standardise the dataset in preparation for further analysis.

4.2.9.1 Confirming inclusion criteria

While the extraction process of SIR data included specifying the criteria of heart failure diagnosis within each patient extracted, there was invariably a mismatch between the data received and the codes found in the patient notes. As a result, we re-applied our inclusion criteria of heart failure read codes to the raw data to exclude patients who did not have a new diagnosis of heart failure.

4.2.9.2 Clinical variables requiring modification

In line with our method of mapping clinical values to each creatinine test, several adjustments needed to be made to accommodate this longitudinal format. These modifications, as well as any special circumstances regarding the processing of individual variables, are described in the following sections.

Smoking status

Determining smoking status was a two-part process. While most binary variables are static e.g. 'Diabetes' will trigger '1' (present) at the point in time of the first clinical code being present in the patient's data and will not change from then on, smoking status is dynamic as a patient may stop smoking. Therefore both 'start' codes and 'stop' codes were incorporated during the timeline such that a positive trigger '1' will be in effect at the time a start code is detected, and will remain in effect in all future time points until a 'stop' code is detected, triggering the negative '0' effect, and vice versa.

Hypertension

Similar to smoking status, this was a dynamic binary variable. Rather than depending on code-triggers however, it used the continuous variable of systolic and diastolic blood pressure as trigger markers. As shown in Appendix 15, the hypertension trigger was set to systolic values > 140 and diastolic values >90.

Anaemia

As above, thresholds were set to trigger the dynamic binary variable of anaemia based on haemoglobin count. The only caveat being that this trigger was also adjusted by the gender variable, setting different thresholds for each. The thresholds were based on the lab reference ranges for Salford Royal Hospital where these samples would have been processed.

LSOA + IMD Decile

To obtain 'IMD Decile' for each patient, we used the GP-level Lower Layer Super Output Area (LSOA), and cross-matched this with look-up tables for IMD decile.[276] This was a proxy value since only GP-level location data was available from SIR rather than the location of individual patients. Since the data spanned the years between 2008 – 2016, we used the 2010 IMD chart to match LSOA to IMD. IMD changes infrequently for each area, so we decided to use the IMDs from an early stage in the dataset, with a view to maximising the exposure time of each patient to the correct IMD while present within the data. A later IMD value may not be as representative and may lead to undue bias, hence this decision.

CKD

To determine stage of chronic kidney disease we used the KDIGO definition of chronic kidney disease.[93] For the initial diagnosis, we looked for an eGFR consistently less than 60 for 6 months. Beyond that point, the patient would trigger a 'CKD flag'. From then onwards, the eGFR value would be correlated to the stage of CKD as per the KDIGO ranges, which is shown in Appendix 15.

AKI Episodes

To calculate the number of episodes of AKI an R script was coded which emulated the national AKI algorithm published by NHS England.[277] The script measures a baseline creatinine as either the median of the last year of the patient's creatinine, or the lowest creatinine within 7 days of the new test. It then makes a comparison each time a new measurement is taken, to check if the new value exceeds 50% of the

baseline, triggering an AKI flag. The number of 'AKI flags' or episodes of AKI within a patient's longitudinal data history is added up cumulatively with each trigger, so that at any time point, it is evident how many previous AKI episodes have been previously recorded.

Medication data

The SIR dataset provides medication data as event codes at the time of dispensing each prescribed medication only, as well as the dose of the prescription. This means that recorded data is limited to prescriptions collected, and does not specify by whom it was collected, whether the patient actually took the medication, nor if the patient was instructed to stop taking the medication.

To address this, a custom algorithm was used to estimate start and stop times of each medication, known as the Research Events Medication Tool, using Perl.[278] This algorithm had to make several assumptions to order the data in a usable manner:

- It was assumed that if a drug was not re-collected after 6 months since last being dispensed, the patient had stopped taking it.
- If a drug had been dispensed that had not been previously prescribed, it was assumed to be a new prescription.
- For drugs that were regularly dispensed, it was assumed that the patient was compliant and continued to take them at the instructed frequency.

This allowed us to record both exposure time to each drug class as well as individual drugs at different doses for each patient longitudinally.

Days since diagnosis

For binary disease variables, it was useful to determine the duration of exposure for each pathology as it may have an additive impact on creatinine over time. For this reason, a supplementary variable of 'Days since diagnosis' was added where possible. This took the difference in number of days between the index point of diagnosis, and each creatinine time point. For this, it was important to consider whether the diagnosis had been made before the start of the study window (01/01/2008). Therefore, for these variables specifically, we used retrospective data before the study window to confirm the binary relation to the disease effect, to ascertain the accuracy of exposure time. The 'Days since diagnosis' column applied to the covariates of atrial fibrillation, diabetes, ischaemic heart disease, peripheral vascular disease, and heart failure.

4.2.9.3 De-duplication of data

The SIR raw data included an extensive amount of duplicated data. This occurred because whenever a patient was admitted to hospital, their inpatient data was copied into the GP systems at various times, up to 30 days after the actual clinical event. On inspection, this seemed to occur whenever a GP in Salford looked back on a patient's medical history from when they were in hospital, which caused a copy of the patient's inpatient data to be inserted into the patient's GP system data at that look-up date. This meant that each patient, especially those with multiple inpatient hospital stays, had various numbers of duplicated clinical events interspersed throughout their medical history. To mitigate this, the included 'source' value for each clinical event was used to identify where the data was sourced from. The copied hospital data was then identified as having a different 'source' value than primary GP data. This duplicated data was then filtered out while leaving the true events intact.

4.2.9.4 Accepted clinical ranges

Interrogation of the dataset revealed various unexpected anomalies within the clinical values extracted. In most instances this manifested in clinical values far exceeding those expected within a normal range, even given the known pathology. For example, in the variable for systolic blood pressure, there existed several values exceeding 100,000 mmHg. This is likely due to coding error at the point of data entry, but highlighted the fact that the raw data required further filtering measures. Figure 4.1 shows a sample of data from the raw dataset, displaying range of values within the systolic blood pressure variable, with a cut-off point of 2000 mmHg.

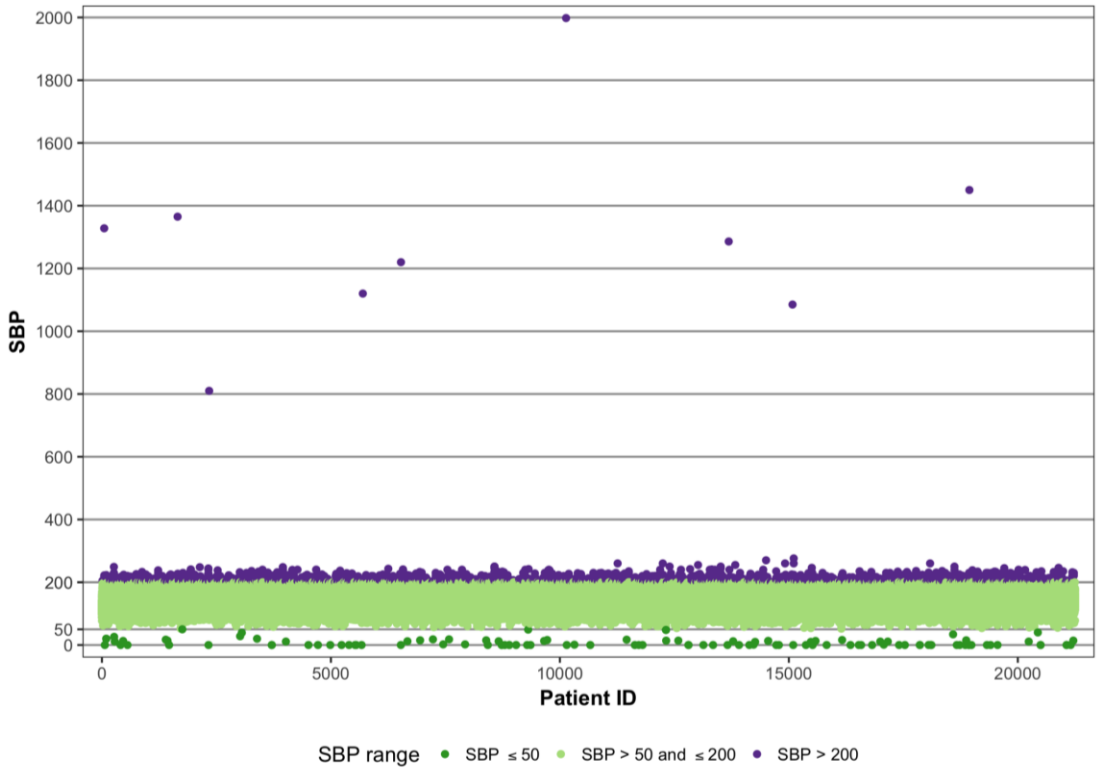

Figure 4.1 Systolic blood pressure from raw SIR data (cut off at 2000 mmHg)

As shown, there are a number of obvious data errors which require further filtering. However, even on closer inspection, there are a multitude of values which exceed 300 mmHg, an unrealistic value in this patient population. Figure 4.2 shows the same sample of data, with a cut-off at 500 mm Hg.

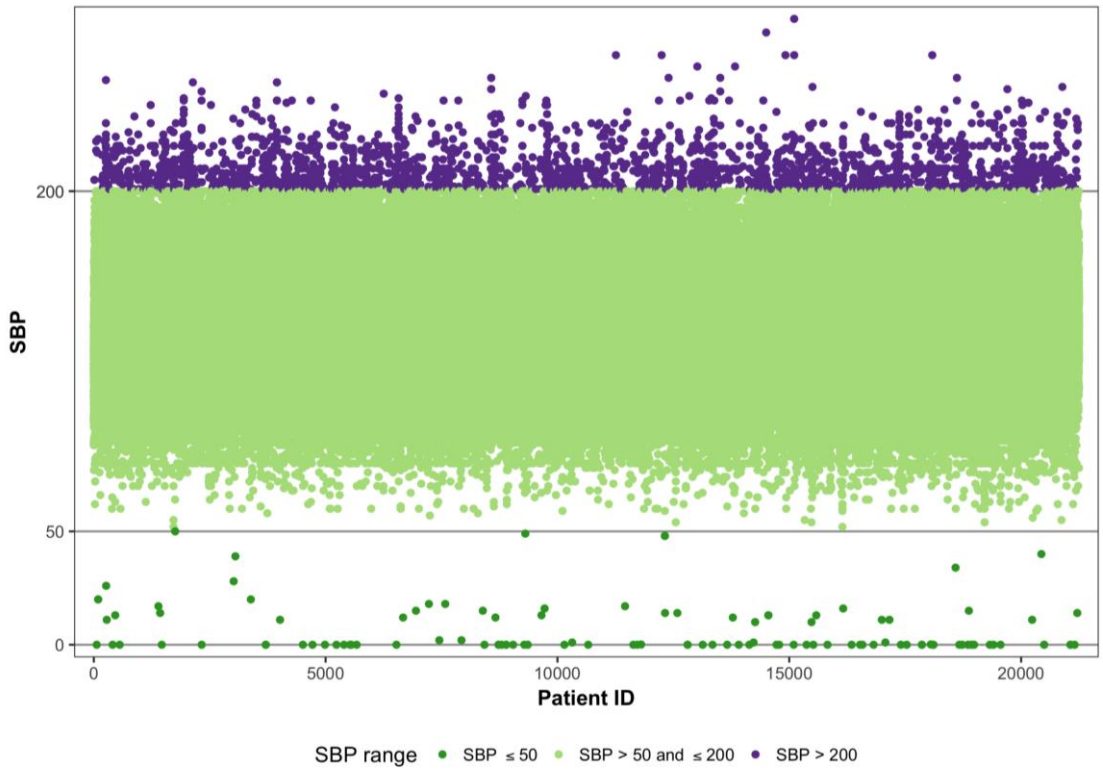

Figure 4.2 Systolic blood pressure from raw SIR data (cut off at 500 mmHg)

As demonstrated, the closer the proximity to normal reference ranges, the more frequent these anomalies appear to exist. Even at the opposite extreme, there are many values which lie below 50 mmHg systolic, at ranges which are not compatible with life. For this reason, continuous variables within the dataset were handled cautiously, and an internal reference range for acceptable values was derived. These thresholds allowed us to ascertain which data points were valid measurements in the context of clinical pathology versus data which was anomalous. The range of accepted clinical values were decided by consensus from the clinical team members in the research group. Values appearing outside these defined thresholds were classed as missing, and

the next latest valid value was used instead. These acceptable value thresholds are defined in Table 4.2.

Table 4.2 Accepted clinical value ranges used for filtering out anomalous data

Variable	**Clinical value range accepted**
BNP	1 – 1000 pg/ml
NTproBNP	1 - 6000 pg/ml
Systolic BP	30 – 300 mm/Hg
Diastolic BP	20 – 200 mm/Hg
Heart Rate	20 – 200 bpm
BMI	10 – 70 kg/m^2
Serum Albumin	10 – 60 g/L
Urine Albumin	0 – 1000 mg/L
Urinary ACR	0 – 3000 mg/mmol
Haemoglobin	30 – 260 g/L
MCV	50 – 150 fL
Serum Potassium	2 – 10 mmol/L
Serum Sodium	80 – 200 mmol/L
Serum Urea (BUN)	(1 – 50 mmol/L)
Serum Uric Acid	1 – 1000 umol/L
Creatinine	18 – 3000 umol/L

Furthermore, where different read codes presented the same variable in different units, efforts were made to standardise each of these values into the most commonly used units appropriately. Values that were outside the accepted range after unit conversion were removed from the data.

4.2.9.5 Multiple measurements per day

While we aligned each clinical variable with the closest future creatinine value, there were many points where a clinical value was measured multiple times in the same day. Since clinical events are only time-stamped according to the day they were activated, it was not possible to determine which value was taken last on that day. In the cases were multiple same-day measurements were found, the mean of the valid clinical values was taken and accepted for that event date. An exception was made for blood pressure recordings, where clinical practice often necessitates repeat measurement whereby the lowest recording is usually accepted, to mitigate the effect of white-coat hypertension.

4.2.9.6 Time Flags

While same-day priorities help us to manage clinical measurements taken within a short time-span of each other, the opposite can also present a problem for standardising data. If measurements are taken very infrequently, such as less than once a year, then the nearest creatinine measurement can be said to have less and less association with this clinical value. The time difference between creatinine and the clinical value in question causes a dissociation which can bias the prediction analysis. Therefore, it was necessary to enforce a limit on the time difference between each clinical event time and the nearest associated future creatinine. Should the limit be exceeded, the clinical

variable would be regarded as ‘missing’ rather than accepting an old value which may no longer be associated with an accurate picture of clinical status for that time point. These limits were decided based on clinical observation of the rate of change over time for each variable and the likely impact on clinical status over the patient’s lifetime. Once the limits were set, data which was older than the associated ‘time flag’ for each creatinine measurement was filtered out. The time limits and justification for each continuous variable are outlined in Table 4.3.

4.2.10 Addressing missingness

For the prediction algorithm to have as much data as possible, each time point required all columns (covariate values) to be complete so that no time points were omitted from the data. Therefore, a complete dataset was needed for the prediction analysis to begin. In order to obtain a complete dataset, it was necessary to impute values that were missing. However, there were different amounts of missing data for each co-variable. The less real data appearing in the dataset for each variable, the less accurate the imputation for that value would be in the context of the longitudinal data. For this reason, we created a threshold value of 5% missingness, beyond which we would omit variables, i.e. if a covariate had over 5% of its data missing, factoring in the time-flags and other processing steps described, it would be excluded from the dataset before imputation. This would ensure that all included variables contained over 95% complete data in order to make the imputation a more accurate estimate.

Table 4.3 Time limits for incorporating old data per clinical value

Variable	Time limit	Clinical Reason
BNP	12 months	Slow rate of change
NTproBNP	12 months	Slow rate of change
Systolic BP	1 month	Rapid rate of change
Diastolic BP	1 month	Rapid rate of change
Heart Rate	1 month	Rapid rate of change
BMI	12 months	Slow rate of change
Serum Albumin	12 months	Slow rate of change
Urine Albumin	12 months	Slow rate of change
Urinary ACR	12 months	Slow rate of change – rarely tested
Haemoglobin	4 months	120-day average turnover for red blood cells
MCV	4 months	120-day average turnover for red blood cells
Serum Potassium	1 month	Rapid rate of change
Serum Sodium	1 month	Rapid rate of change
Serum Urea (BUN)	1 month	Rapid rate of change – changes with fluid status
Serum Uric Acid	12 months	Slow rate of change

4.2.11 Pre-feature selection exclusions

In addition to variables excluded on the basis of missing data, several other covariates were omitted at this stage in order to prepare the dataset for the correlation study. Since the output variable was log(creatinine), all other variables that were derived from creatinine would have direct correlation with the output and would therefore have no value in either the correlation study or the predictive algorithm. These were therefore omitted. In addition, there were several data columns that were merely informative and not useful for correlation analysis such as date-flags related to the time limits described previously, which were also omitted at this stage. The full list of omissions and the reason for them can be found in Appendix 16.

4.2.12 Imputation via Random Forest

The remaining included columns for the imputation step are recorded in Appendix 17. The Random Forest method was used to impute any remaining missing data (missForest package in R).[216] This method is classed as single imputation can be as effective as multiple imputation while preventing over-fitting of the imputed variables. Random forest methods use all the covariates of real data to create new imputed values for the missing data, and therefore the processing time is proportional to both the number of values and the number of covariates in the dataset.[279] A single imputation method was selected mainly due the constraints of the size of the data, and the number of different covariates involved which would have made multiple imputation impractical.[280]

4.2.13 Splitting the dataset

The complete dataset was, for the purpose of analysis, split into two:

Training set – Two-thirds of the data would be used for the purpose of the correlation study as well as training the machine learning predictive algorithm.

Test set – One-third of the data would be withdrawn from the dataset and kept for validation of the completed predictive algorithm after training had been complete.

Dataset splitting for testing and training processes is established practice in machine learning algorithm generation.[281] The extent of the split varies between methodologies. For simple algorithms requiring relatively few outputs, many studies suggest an 80-20 split based on the Pareto principle,[282] since less of the sample would be required to test the performance of the algorithm in a way that would be representative. However, with longitudinal studies which require multiple inputs and have a continuous output over time, the required testing sample increases in order to ensure validity of the performance. Similar studies have used a split up to 50-50.[283] For this study, with a relatively low patient count, we wanted to maximise the available data used for training while ensuring a sufficient test sample for performance evaluation, so we opted to split the dataset into thirds, using two-thirds for training and one-third for testing.

To conduct the split, patients were grouped by the general practice from which their data originated, and then the dataset was randomly split using their 'Practice ID', i.e. $1/3^{rd}$ of the GP groups were set aside for the test set and $2/3^{rd}$ of the GP groups went into the training set.

4.2.14 Variable correlation study (Feature selection)

The purpose of this study was to identify which of our covariates is most important for predicting creatinine over time. This correlation analysis, hereby termed ‘feature selection’ was a process used to ultimately determine which covariates are most relevant to include in a predictive model of creatinine and which ones can be cut out. In this way, the covariates or ‘features’ that are most informative are ‘selected’ out.

Having obtained the processed and complete test dataset, linear mixed model regression analysis[284] was carried out with pairwise correlation between each individual variable and the output of log(creatinine). Each regression used the fixed effects of age at heart failure diagnosis, time since heart failure, and gender, with the random effect of Patient ID. Combining both age at heart failure, and time since heart failure, gives both an indicator of time as well as exposure time to heart failure to make the correlation more relevant for this patient cohort. This also standardises each patient’s start point in the data, wherein heart failure exposure time = 0, to compare the creatinine trends between patients more effectively. Since this methodology involves a large number of tests due to the high number of covariates, Benjamini-Hochberg (BH) p-value corrections were used to avoid false positive results from multiple testing, while also reducing the rate of false negative results compared to other correction methods such as Bonferroni.[285] The choice to use BH was implemented because we would be making feature selection decisions based on ranking rather than p-value thresholds, and therefore the effect of type 1 errors on our outputs would be diminished. In other words, a significant feature does not guarantee its inclusion into the algorithm, and so this allowed us flexibility to correct for false negatives more stringently.[286, 287]

This method provided simple and rapid correlation values that can be easily contrasted and compared against each covariate. Furthermore, it was well suited to longitudinal data such as in this dataset.[288-290] However, there were a few notable drawbacks, including the fact that non-linear correlations cannot be detected unless pre-specified. It also assumed that each covariate was separate and independent of each other, which, as in most cases with medical covariates, is not the case since many co-morbidities interact with each other, such as diabetes and chronic kidney disease.

4.3 Results of dataset generation

4.3.1 Patient data retention

The original dataset provided by SIR numbered 21,249 patients with data ranging from 1990 to 2016. After excluding all patients that did not have selected heart failure read codes, 7703 patients remained. After the inclusion criteria for age, index diagnosis of heart failure after 2018, and 2+ creatinine values after heart failure diagnosis, as well as de-duplication and time-limit processing were applied, the heart failure cohort numbered 3822 patients. This was the dataset used for cohort analysis. The post-dialysis creatinine values were then removed, excluding a further 22 patients, leaving 3800 patients for the imputation step, and then splitting. The patient retention flowchart is shown in Figure 4.3.

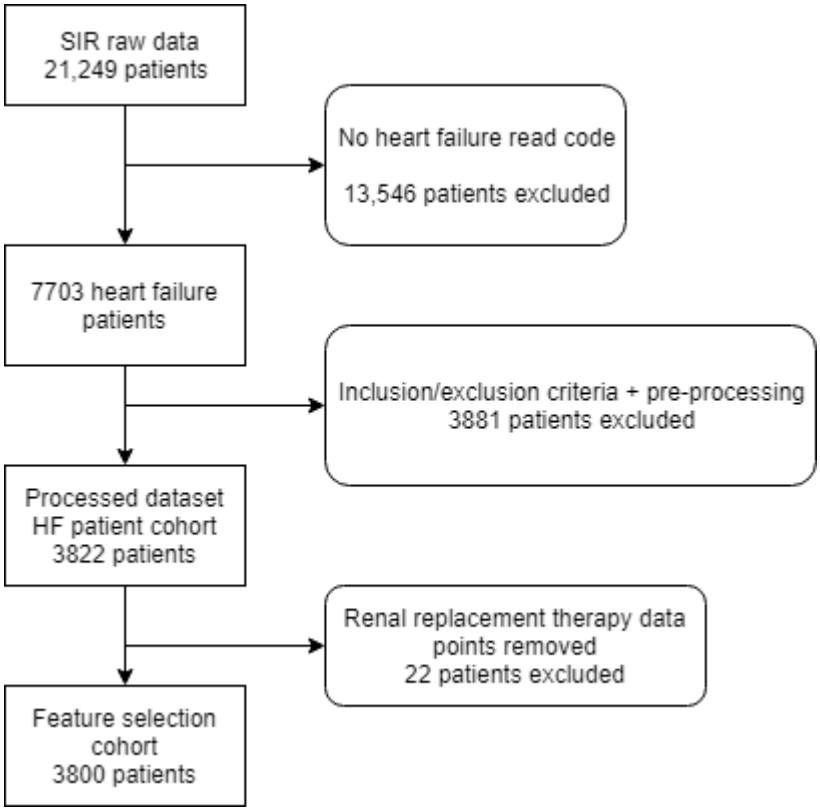

Figure 4.3 Flowchart of patient selection throughout study

4.3.2 Post-split data

The complete dataset of 3800 patients within 50 practices was split into a training set with two-thirds of the practices and a test set with one-third of the practices. The resulting split was as follows:

- Training set: 2704 patients within 34 Practice IDs – to be used for building a predictive algorithm
- Test set: 1096 patients within 16 Practice IDs – to be used for validating the established algorithm

Practice ID was used as a method of randomly splitting the data evenly since it was important to test how well the algorithm would fit with new patient populations in

separate areas. Using patients with the same Practice ID (and thus within the same local area) in both the training and test sets was avoided, in order to more easily identify whether overfitting was present in the predictive algorithm generated. By allowing the test dataset to include wholly patients from different geographical locations, the algorithm could be tested in a 'new' environment, to better assess its applied predictive ability on different populations.

4.3.3 Variables excluded due to missing data

As shown in Appendix 16, the following initial variables were excluded due to extensive missing data:

- BNP 92.9% missing
- NT pro-BNP 98.7% missing
- CLD 97.9% null
- Nephrectomy 100% null
- Renal malignancy 99.4% null
- Renal transplant 99.7% null
- Heart rate 83.2% missing
- ACR 44% missing
- Urine albumin 45% missing
- Uric acid 70.8% missing

As discussed previously, we set a threshold for missingness of values for continuous variables of over 5%. For binary variables (mostly co-morbidities that were either present or not) we excluded variables that had over 95% null, as it would not represent a sufficient sample within the population to measure the effect on creatinine trend.

4.3.4 Results of imputation

Random Forest (‘missForest’ package within the statistical programming platform R) was run for 10,000 iterations and converged after 9. The total computational time for this was 3 days. The continuous variables imputed included potassium, IMD, BMI, sodium, albumin, MCV, BP, PP and Hb. The results of the imputation as well as the error values are shown in Table 4.4. The error of imputation is an aggregate product of the standard error for each iteration of the multiple imputation process, and is affected by the number of other missing features in each case. The closer the error value to 0, the better the estimate created by the imputation algorithm.[291] As shown, the estimates for potassium and IMD had an error value <1, likely owing to the low degree of variance within the real data of these covariates, which is due in part to the low range of values within these categories.

Table 4.4 Results of 10,000 imputation iterations via Random Forest

Feature	Error	% missing from data	No. values missing	Variance of true values	Variance of imputed values	True: Imputed variance ratio
Serum Potassium	0.192	0.006%	5	0.370	0.005	74.00
IMD Decile 2010	0.928	0.850%	687	5.161	0.202	25.55
BMI	7.886	1.197%	968	47.870	10.388	4.61
Serum Sodium	8.852	0.001%	1	20.105	NA	NA
Serum Albumin	9.259	0.074%	60	36.308	15.045	2.41
MCV	12.570	0.090%	73	44.081	1.272	34.65
SBP	16.290	0.239%	193	395.080	22.207	17.79
DBP	19.050	0.241%	195	141.758	17.003	8.34
Pulse Pressure	22.080	0.241%	195	293.841	15.769	18.63
Haemoglobin	137.800	0.057%	46	576.989	42.418	13.60

To further explore the source of the high error values for variables other than potassium and IMD, the following validation checks were done:

A) Pre-imputation check

This involved shuffling the input columns before imputation to ensure the values were not processed in the same order each iteration. In addition, the random seed was changed before each imputation run. These checks did not lower the error rates of imputed data.

B) Post-imputation checks

This involved checking the variance of the real data compared to the imputed data for each variable. Since random forest uses the pattern of other covariates within the same dataset to estimate missing values, this check could pick up whether there was little correlation between the imputed variable and the others in the dataset, thus leading to a biased estimation. Prominently, it was found that the drug category and dose variables had little to no correlation with any of the missing variable data and so were less utilised in the imputation process.

Overall, after excluding variables with high numbers of missing data, the remaining gaps within the dataset were relatively minor. In this context, the imputation was able to provide a workable estimate for these gaps and provide a complete dataset with minimal bias for the feature selection step.

4.4 Characteristics of the study population

4.4.1 Patient follow up

As shown in Table 4.5 below, the mean follow-up time for patients within the 8.5-year study window was 1012 days, around 2.8 years. However, there was a wide variability between patients in terms of follow up with an SD value of 842 days, up to 2.3 years. Therefore, the descriptive findings throughout the longitudinal data should be interpreted in light of this average timespan. The average number of data points or individual creatinine measurements separated by time for each patient was 20.7, but again with wide variability (SD 20.3). Furthermore, the average number of days between creatinine measurements for each patient was around 7 weeks (51 days) yet the SD value was around 14 weeks (98.6 days), over twice the actual mean, indicating high variability.

Table 4.5 Follow up time for patients within each subset during the study window

Dataset	Mean follow up time span (+/- SD) [days]	Mean number of time points (+/- SD)	Monitoring frequency (+/- SD) [days]
Whole dataset	1012.8 (842.2)	20.7 (20.3)	51.38 (98.6)
Training dataset	987.7 (834.1)	20.9 (20.6)	49.6 (96.9)
Test dataset	1074.5 (859.1)	20.2 (19.5)	56.0 (102.8)

4.4.2 Frequency of monitoring of renal function with different CKD stages

Monitoring frequency differed on average according to CKD stage as shown in Table 4.6. Patients with eGFR values 60 or more appeared to have similar frequencies of monitoring with an average interval time of around 70 days (72 days for eGFR 60-90 and 68 days for eGFR 90+) or 10 weeks. This is a greater length of time compared to the average interval time of 51 days or 7 weeks for the whole dataset. The eGFR category of 45-59 (the equivalent of CKD stage 3a) has an average interval time of 55 days which is closer to the whole dataset average and lower than the high eGFR categories by 3 weeks. The interval time for patients with an eGFR of 30-44 (CKD 3b) was lower still at 42 days average, or 6 weeks. CKD stage 4 (eGFR between 15-19) patients had an average interval monitoring time of 30 days (4.3 weeks), and for those with stage 5 (eGFR <15) it was more than twice as frequent, with an interval time of just 11 days (1.7 weeks).

Table 4.6 Comparison of mean frequency of creatinine monitoring between patients at different stages of CKD

CKD-EPI eGFR	Equivalent CKD Stage	Monitoring frequency mean [days]
0-14	5	11.24
15-29	4	26.95
30-44	3b	41.74
45-59	3a	54.58
60-90	2	71.73
over 90	1	67.95

Therefore, it can be seen that monitoring frequency differs greatly between different reported CKD stages, and as the eGFR decreases for each patient, the frequency of their creatinine monitoring increases, especially so with CKD 4 and 5.

4.4.3 Descriptive statistics

Tables 4.7 and 4.8 summarise the characteristics of the heart failure patient cohort used in this study, as well as the frequency of occurrence of their co-morbidities, medications and mean clinical values, subset by gender. This data table shows the status of the data pre-imputation and prior to removing the renal replacement therapy creatinine values.

When calculating the mean values for continuous variables over a longitudinal dataset, the mean of all the values of each patient were calculated individually, and then the mean of these means was calculated and presented. For categorical variables, the count represents each patient who fitted the category at any time point within the study window.

Table 4.7 Descriptive statistics for demographic and clinical parameters of heart failure patient cohort, subset by gender

	All patients			Male			Female		
	value	**SD**	**Freq (%)**	**value**	**SD**	**Freq (%)**	**value**	**SD**	**Freq (%)**
n	3822	-	-	2094	-	-	1728	-	-
Mean age	74.60	12.70	-	72.53	12.87	-	77.11	12.03	-
Median age	76.47	-	-	74.33	-	-	83.26	-	-
Mean age at heart failure diagnosis	73.08	12.92	-	70.94	13.05	-	75.68	12.27	-
Median age at heart failure diagnosis	75	-	-	72.50	-	-	77	-	-
Mean heart failure exposure time (days)	560.16	489.46	-	586.62	489.00	-	528.1	488.25	-
Median heart failure exposure time (days)	428.80	-	-	465.14	-	-	385.34	-	-
GENDER									
Women	1728	-	45.21%	-	-	-	-	-	-
Men	2094	-	54.79%	-	-	-	-	-	-
ETHNICITY									
Total recorded	3749	-	98.09%	2054	-	98.09%	1695	-	98.09%
Missing data	73	-	1.91%	40	-	1.91%	33	-	1.91%
White	3688	-	98.37%	2011	-	96.04%	1677	-	97.05%
Mixed background	5	-	0.13%	5	-	0.24%	0	-	0%
Asian	26	-	0.69%	18	-	0.86%	8	-	0.46%
Afro-Caribbean	18	-	0.48%	10	-	0.48%	8	-	0.46%
Chinese/ any other ethnic groups	12	-	0.32%	10	-	0.48%	2	-	0.12%
SOCIOECONOMIC DECILE									
Total recorded	3792	-	99.22%	2077	-	99.19%	1715	-	99.25%
Missing data	30	-	0.78%	17	-	0.81%	13	-	0.75%
Mean	3.28	2.34	-	3.32	2.38	-	3.24	2.29	-
Median	3	-	-	3.00	-	-	3	-	-

	All patients			Male			Female		
	value	**SD**	**Freq (%)**	**value**	**SD**	**Freq (%)**	**value**	**SD**	**Freq (%)**
1 (most deprived)	1247	-	32.89%	677	-	32.60%	570	-	33.24%
2	533	-	14.06%	308	-	14.83%	225	-	13.12%
3	475	-	12.53%	238	-	11.46%	237	-	13.82%
4	532	-	14.03%	285	-	13.72%	247	-	14.4%
5	341	-	8.99%	187	-	9.00%	154	-	8.98%
6	252	-	6.65%	145	-	6.98%	107	-	6.24%
7	96	-	2.53%	52	-	2.50%	44	-	2.57%
8	198	-	5.22%	116	-	5.58%	82	-	4.78%
9	73	-	1.93%	41	-	1.97%	32	-	1.87%
10 (least deprived)	45	-	1.19%	28	-	1.35%	17	-	0.99%
SYSTOLIC BP (mmHg)									
Total recorded	3820	-	99.95%	2093	-	99.95%	1727	-	99.94%
Missing data	2	-	0.05%	1	-	0.05%	1	-	0.06%
Mean	127.69	14.73		126.58	14.17	-	129.05	15.28	-
Median	127.35	-	-	126.43	-	-	128.70	-	-
< 90	350	-	9.16%	200	-	9.56%	150	-	8.69%
> 140	2103	-	55.05%	1102	-	52.65%	1001	-	57.96%
DIASTOLIC BP (mmHg)									
Total recorded	3820	-	99.95%	2093	-	99.95%	1727	-	99.94%
Missing data	2	-	0.05%	1	-	0.05%	1	-	0.06%
Mean	71.55	8.88		71.77	9.13	-	71.28	8.57	-
Median	71.15	-	-	71.50	-	-	70.96	-	-
< 60	1558	-	40.79%	835	-	39.89%	723	-	41.86%
> 90	748	-	19.58%	395	-	18.87%	353	-	20.44%

	All patients			Male			Female		
	value	**SD**	**Freq (%)**	**value**	**SD**	**Freq (%)**	**value**	**SD**	**Freq (%)**
Pulse Pressure (mmHg)									
Total recorded	3820	-	99.95%	2093	-	99.95%	1727	-	99.94%
Missing data	2	-	0.05%	1	-	0.05%	1	-	0.06%
Mean	56.13	12.75		54.79	12.19	-	57.77	13.23	-
Median	55.07	-	-	54	-	-	57	-	-
< 30	591	-	15.47%	342	-	16.34%	249	-	14.42%
> 50	3404	-	89.11%	1833	-	87.58%	1571	-	90.97%
HEART RATE									
Total recorded	642	-	16.8%	369	-	17.62%	273	-	15.80%
Missing data	3180	-	83.2%	1725	-	82.38%	1455	-	84.20%
Mean	75.25	13.58	-	73.47	12.53	-	77.72	14.58	-
Median	73.75	-	-	72.13	-	-	76	-	-
<60	153	-	23.83%	96	-	26.02%	57	-	20.88%
>100	65	-	10.12%	29	-	7.86%	36	-	13.19%
BMI									
Total recorded	3794	-	99.27%	2084	-	99.52%	1710	-	98.96%
Missing data	28	-	0.73%	10	-	0.48%	18	-	1.04%
Mean	28.13	6.61	-	28.32	5.97	-	27.91	7.31	-
Median	27.22	-	-	27.55	-	-	26.66	-	-
Underweight (<18.5)	324	-	8.54%	116	-	5.57%	208	-	12.16%
Normal (18.5 - 25)	599	-	15.79%	866	-	41.55%	839	-	49.06%
Overweight (25 - 30)	1209	-	31.87%	1163	-	55.81%	786	-	45.96%
Obese (>30)	1662	-	43.81%	925	-	44.39%	737	-	43.1%
SMOKING									

	All patients			Male			Female		
	value	**SD**	**Freq (%)**	**value**	**SD**	**Freq (%)**	**value**	**SD**	**Freq (%)**
Total recorded	3822	-	100.00%	2094	-	100%	1728	-	100.00%
Missing data	0	-	0.00%	0	-	0%	0	-	0.00%
Never smoked	2826	-	73.94%	1571	-	75.02%	1389	-	80.38%
Ever-smoked?	862	-	22.55%	523	-	24.98%	339	-	19.62%
OTHER CO-MORBIDITIES									
Anaemia	3355	-	87.78%	1874	-	89.49%	1481	-	85.71%
Atrial Fibrillation	1541	-	40.32%	834	-	39.83%	707	-	40.91%
Diabetes	1129	-	29.54%	631	-	30.13%	498	-	28.82%
Hypertension	2184	-	57.14%	1151	-	54.97%	1033	-	59.78%
Ischaemic heart disease	2253	-	58.95%	1304	-	62.27%	949	-	54.92%
Peripheral vascular disease	1473	-	38.54%	787	-	37.58%	686	-	39.70%
Renal replacement therapy	42	-	1.10%	25	-	1.19%	17	-	0.98%
Mortality	984	-	25.75%	524	-	25.02%	460	-	26.62%
MEDICATIONS									
ACE Inhibitors	2504	-	65.52%	1491	-	71.2%	1013	-	58.62%
Angiotensin receptor blockers	809	-	21.17%	415	-	19.82%	394	-	22.8%
Either ACEi or ARB	2928	-	76.61%	1693	-	80.85%	1235	-	71.47%
Aldosterone antagonists	1076	-	28.15%	628	-	29.99%	448	-	25.93%
Loop Diuretics	2521	-	65.96%	1280	-	61.13%	1241	-	71.82%
Thiazide diuretics	1109	-	29.02%	604	-	28.84%	505	-	29.22%
Antimicrobials	409	-	10.7%	190	-	9.07%	219	-	12.67%
Immunosuppressants	52	-	1.36%	26	-	1.24%	26	-	1.5%
NSAIDs	505	-	13.21%	270	-	12.89%	235	-	13.60%
Other nephrotoxins	14	-	0.37%	7	-	0.33%	7	-	0.41%

Table 4.8 Descriptive statistics of biochemical and renal parameters of heart failure patient cohort, subset by gender

	All patients			Male			Female		
	value	**SD**	**Freq (%)**	**value**	**SD**	**Freq (%)**	**value**	**SD**	**Freq (%)**
HAEMOGLOBIN (g/L)									
Total recorded	3821	-	99.97%	2093	-	99.95%	1728	-	100%
Missing data	1	-	0.03%	1	-	0.05%	0	-	0%
Mean	117.59	18.66	-	120.32	20.39	-	114.31	15.74	-
Median	116.80		-	120.17	-	-	113.85	-	-
< 115 (F lower limit)	3122	-	81.71%	-	-	-	1481	-	85.71%
< 130 (M lower limit)	3522	-	92.17%	1874	-	89.54%	-	-	-
>165 (F upper limit)	257	-	6.73%	-	-	-	49	-	2.84%
>180 (M upper limit)	38	-	0.99%	29	-	1.39%	-	-	-
MCV (fL)									
Total recorded	3819	-	99.92%	2091	-	99.86%	1728	-	100%
Missing data	3	-	0.08%	3	-	0.14%	0	-	0%
Mean	90.20	5.68	-	90.47	5.45	-	89.87	5.92	-
Median	90.22	-	-	90.60	-	-	89.78	-	-
< 80	604	-	15.82%	270	-	12.91%	334	-	19.33%
> 100	650	-	17.02%	351	-	16.79%	299	-	17.30%
SERUM SODIUM (mmol/L)									
Total recorded	3822	-	100%	2094	-	100%	1728	-	100%
Missing data	0	-	0%	0	-	0%	0	-	0%
Mean	138.84	3.25	-	138.95	3.18	-	138.71	3.33	-
Median	139.33	-	-	139.42	-	-	139.23	-	-

	All patients			Male			Female		
	value	**SD**	**Freq (%)**	**value**	**SD**	**Freq (%)**	**value**	**SD**	**Freq (%)**
< 133	1216	-	31.82%	605	-	28.89%	611	-	35.36%
> 146	514	-	13.45%	278	-	13.28%	236	-	13.66%
SERUM POTASSIUM (mmol/L)									
Total recorded	3822	-	100%	2094	-	100%	1728	-	100%
Missing data	0	-	0%	0	-	0%	0	-	0%
Mean	4.35	0.38	-	4.38	0.37	-	4.31	0.39	-
Median	4.35	-	-	4.37	-	-	4.31	-	-
< 3.5	1250	-	32.71%	572	-	27.32%	678	-	39.24%
> 5.3	1208	-	31.61%	645	-	30.8%	563	-	32.58%
SERUM CREATININE (umol/L)									
Total recorded	3822	-	100%	2094	-	100%	1728	-	100%
Missing data	0	-	0%	0	-	0%	0	-	0%
Mean	106	59.63	-	114.44	64.22	-	96.15	51.82	-
Median	91.51	-	-	97.89	-	-	83.26	-	-
< 44 (F lower limit)	275	-	7.2%	-	-	-	204	-	11.81%
< 62 (M lower limit)	1155	-	30.22%	366	-	17.48%	-	-	-
> 97 (F upper limit)	2617	-	68.47%	-	-	-	1069	-	61.86%
> 115 (M upper limit)	2009	-	52.56%	1181	-	56.4%	-	-	-
SERUM UREA (mmol/L)									
Total recorded	3822	-	100%	2094	-	100%	1728	-	100%
Missing data	0	-	0%	0	-	0%	0	-	0%
Mean	9.08	4.62	-	9.08	4.7	-	9.07	4.51	-
Median	7.78	-	-	7.69	-	-	7.84	-	-

	All patients			Male			Female		
	value	**SD**	**Freq (%)**	**value**	**SD**	**Freq (%)**	**value**	**SD**	**Freq (%)**
< 2.5	174	-	4.55%	83	-	3.96%	91	-	5.27%
> 7.8	2956	-	77.34%	1582	-	75.55%	1374	-	79.51%
SERUM ALBUMIN (g/L)									
Total recorded	3820	-	99.95%	2093	-	99.95%	1727	-	99.94%
Missing data	2	-	0.05%	1	-	0.05%	1	-	0.06%
Mean	39.16	4.68	-	39.61	4.69	-	38.61	4.61	-
Median	39.80	-	-	40.31	-	-	39.31	-	-
< 35	1758	-	46.02%	887	-	42.38%	871	-	50.43%
> 50	75	-	1.96%	47	-	2.25%	28	-	1.62%
URINARY ACR (mg/mmol)									
Total recorded	2137.00	-	55.91%	1148	-	54.82%	989	-	57.23%
Missing data	1685.00	-	44.09%	946	-	45.18%	739	-	42.77%
Mean	17.72	62.73	-	18.11	61.71	-	17.28	63.89	-
Median	2.24	-	-	1.99	-	-	2.42	-	-
> 3.5 (F upper limit)	943.00	-	44.13%	-	-	-	458	-	46.31%
> 2.5 (M upper limit)	1095.00	-	51.24%	557	-	48.52%	-	-	-
ACR grade 2: >3	1009.00	-	47.22%	523	-	45.56%	486	-	49.14%
ACR grade 3: >30	247.00	-	11.56%	142	-	12.37%	105	-	10.62%
CHRONIC KIDNEY DISEASE									
MDRD CKD stage 3-5 (eGFR <60)	2030.00	-	53.11%	946	-	45.18%	1084	-	62.73%
MDRD CKD stage 4-5 (eGFR <30)	998	-	26.11%	476	-	22.73%	522	-	30.21%
MDRD CKD stage 5 (eGFR <15)	271	-	7.09%	136	-	6.49%	135	-	7.81%
CKD-EPI CKD stage 3-5 (eGFR <60)	1967	-	51.47%	936	-	44.7%	1031	-	59.66%

	All patients			Male			Female		
	value	**SD**	**Freq (%)**	**value**	**SD**	**Freq (%)**	**value**	**SD**	**Freq (%)**
CKD-EPI CKD stage 4-5 (eGFR <30)	1063	-	27.81%	508	-	24.26%	555	-	32.12%
CKD-EPI CKD stage 5 (eGFR <15)	311	-	8.14%	159	-	7.59%	152	-	8.80%
Acute kidney injury									
Patients with AKI	1839	-	48.12%	904	-	43.17%	935	-	54.11%
No. of episodes (Mean)	1.12	2.86	-	1.02	2.9	-	1.24	2.81	-
No. of episodes (Median)	2	-	-	0	-	-	0.33	-	-

4.4.4 Demographics

This adult chronic heart failure patient cohort was comprised of a total of 3822 patients, with 45% female and 55% male distribution. The average age of all patients was around 75, and the mean age at heart failure diagnosis was 73. Of note, the mean age of diagnosis for male patients was 71 and for female patients was 76. As a consequence, mean heart failure exposure time was less in women (528 days) compared to men (587 days), and in addition, the female cohort was older.

Ethnicity was recorded in a total of 3749 patients. Out of these, 3688 (98%) of them were categorised as 'White', with 61 patients (less than 2%) classed within other ethnicity categories.

IMD was matched to a proxy GP-level LSOA so there was good a capture rate for this, with data recorded in 99% of patients. The mean IMD decile value was 3 for this patient cohort. Decile 1, the most deprived socio-economic category numbered 1247 patients, around one third of the whole cohort (33%). IMD Deciles 1 through 4 were the most prevalent in this data, with deciles 2-4 each numbering about 14% of patients. Decile 10, the most affluent category comprised only 1% of the population. These proportions remained consistent in both male and female subsets. It is important to note that these deciles were based on the GP practice location and not individual patient postcodes so there could in fact be a wide range of IMDs attending one GP.

4.4.5 Cardiovascular covariates

The mean systolic BP was 127. Over half the cohort (55%) were recorded as having hypertension stage 1 (SBP>140) at some point within the study window. The mean diastolic blood pressure was 71. In contrast to the high rates of systolic hypertension,

only 20% of patients had diastolic BP >90. The pulse pressure showed a mean of 56, with 89% of the cohort having a pulse pressure over 50 at any one point in the study, indicating a preponderance for widened pulse pressure in this population.

The heart rate poorly recorded in primary care data, with only 17% capture rate and 83% patients having no recorded heart rate. In those that were recorded, the mean value was 75. Most patients fell within the range of normal HR variation with only 34% abnormal (24% patients recorded bradycardia with a HR <60 and 10% patients had tachycardia with a HR >100).

BMI was well recorded and showed a mean value of 28 and median of 27 across patient groups in males and females. However, there are divergent figures across the weight categories between the gender subsets. The underweight category (BMI<18.5) was higher in females (12%) than in males (6%). There was also a greater proportion of patients with BMI recorded in the overweight range (BMI 25-30) in males (56%) rather than females (46%), but the proportion of obese readings (BMI>30) from patients were roughly the same between male and female groups (44% and 43% respectively).

Out of all patients, 23% were recorded as having smoked in the past. Though this data is based on GP documentation taken from patient history. The proportions for male and female groups were 23% and 20% respectively.

4.4.6 Renal and biochemical covariates

There was good capture rate for Hb values for each patient with only one patient having missing data. There were high rates of recorded anaemia in both gender subgroups during the study window, with around 90% of male patients (Hb <130) and 86% of

female patients (Hb <115) classed within this category. The MCV average between all groups was 90 with a SD value of around 5.5, indicating that there was little variability and that most values lied within normal range of 80-100. There was a slightly greater proportion of microcytosis (MCV<80) in the female group vs the male group (19% vs 13%).

All patients in the dataset had recorded data on sodium, potassium, creatinine and urea values as these measures make up part of the same panel of biochemistry tests. The mean sodium was 139 mmol/L, consistent throughout groups. There were moderate rates of hyponatraemia (Na < 133), with a greater proportion in females (35%) than in males (29%). The mean serum potassium value was 4.35 mmol/L with SD of 0.38 which was mostly consistent throughout. However, a similar trend to sodium was seen in this variable in that there were higher rates of hypokalaemia in females (39%) compared to males (27%). The rates of hyperkalaemia between male and female groups were 31% and 33% respectively, with an overall average of 32%, showing that a third of patients had high potassium at some point in the study. The mean creatinine was 106 umol/L between groups. In the male group 56% had creatinine over the upper limit of normal for men (>115), and in the female group 62% had a measurement over the upper limit for women (>97).

The mean serum albumin was 39 (SD 4.6) g/L and the normal range for this clinically is between 35 – 50 g/L. However, 50% of female patients within the study fell to below 35 g/L at some point in the study, and for male patients, this proportion was 42%.

Urinalysis readings were largely poorly recorded or not up to date, with 44% of patients having missing urinary ACR data. The upper limit of ACR is 2.5 mg/mmol for males and 3.5 mg/mmol for females. Of the 2137 patients without missing data, this upper limit was exceeded in 46% of female patients and in 49% of male patients.

Patient eGFR values were calculated manually using both MDRD and CKD-EPI formulas. In the whole dataset, over half the patients were recorded as acquiring CKD 3 or higher (MDRD = 53%, CKD-EPI = 51%). While MDRD formula recorded higher rates of CKD 3+, CKD-EPI formula classified more patients in CKD 5 than MDRD (8% vs 7%). The number of patients with a recorded AKI episode from the data was 1839, around 48% of the cohort. The proportion in the female group was higher than that in the male group (54% vs 43%). The mean number of AKI episodes was 1.02 in the male group and 1.24 in the female group.

4.4.7 Other comorbidities

Atrial fibrillation was found to be present in 40% of the cohort, with numbers consistent between males and females. Diabetes was recorded in around 30% of the population. Ischaemic heart disease was found in 59% of the whole cohort, though there was a difference between male and female groups, 62% and 55% respectively. Peripheral vascular disease was noted in 39% of the cohort, consistent between gender groups. A total of 42 patients in the dataset had renal replacement therapy, comprising around 1% of the study group (25 male and 17 female).

Mortality read codes were found in 984 patients indicating that around 26% of the cohort died during the study window. There were roughly similar proportions of deaths between male and female groups (25% and 27% respectively), though we were not able to gain access to linked data pertaining to cause of death in this study.

4.4.8 Medication

4.4.8.1 Heart failure treatment

In this cohort, we investigated the rates of common classes of medications prescribed for each patient. Out of all patients only 65% were recorded as ever having been prescribed ACE inhibitors, the most commonly considered first line treatment. The proportions differed between genders, with 71% male patients, compared to 59% female patients prescribed ACE inhibitors. The proportion of patients on ARBs, the most common second line treatment often given for patients intolerant of ACE inhibitors, was 21%. The rates were similar for male and female groups for ARBs. The total incidence of ARB and ACEi prescriptions combined was 77%, with a 10% higher proportion in men than women (81% vs 71% respectively).

A total of 28% of patients were reported to be prescribed aldosterone antagonists, a further adjunct to heart failure therapy, with minor difference between gender groups. Loop diuretics, which are often used for symptomatic control and are linked to reduced renal function, showed a more marked difference between gender groups, being present in 61% of males and 72% of females in the group, giving a total of 66% of the cohort. Thiazide diuretics in contrast were prescribed to 29% in total with little difference between groups.

4.4.8.2 Other medications

This category relates to nephrotoxic medications of various classes. Appendix 14 includes full listings of the medications within these classes. The antimicrobials known to be harmful to renal function were found in the read codes of 11% of the total cohort, 9% in males and 13% in females. Immunosuppressant medication with renal effects were found in only 1% of the population, with similar numbers between genders.

NSAIDs were found in 13% of all patients, again with very little difference in proportion between groups. From our miscellaneous category of nephrotoxins that do not fit the other medication classes, only 14 patients were found to have these in their data, making up 0.4% of the cohort.

4.5 Feature selection results: Clinical correlates with renal function over time

Table 4.9 shows the results of the linear mixed model pairwise regression, comparing the p-value for the association of log(creatinine) with the other covariates by comparing a null model versus a feature model. The likelihood ratio was used for model comparison to create a p-value to estimate by what extent the feature model outperformed the null model.

Null model:

log(creatinine) ~ age at heart failure diagnosis + time since heart failure diagnosis + gender + (1|Patient ID)

Feature model:

log(creatinine) ~ age at heart failure diagnosis + time since heart failure diagnosis + gender + (1|Patient ID) + [covariate tested]

Table 4.9 Results of feature selection study between covariates and log(creatinine)[1]

Variable	BH corrected p value training set	P value training set	BH corrected p value test set	p value test set	BH corrected p value whole SIR	p value whole SIR
BUN (urea)	1.00e-246	< 1e-246	1e-207	2.8e-209	< 1e-303	< 1e-303
Serum potassium	1.00e-246	< 1e-246	< 1e-207	< 1e-207	< 1e-303	< 1e-303
Loop diuretics category	9.9e-169	5.4e-170	1.2e-107	5.7e-109	4.1e-269	2.2e-270
Antimicrobials category	3e-117	1.8e-118	5.5e-60	4.5e-61	5.9e-160	4.2e-161
Aldosterone antagonists category	2.8e-111	1.9e-112	1.1e-57	9.9e-59	1.6e-167	1.1e-168
Serum albumin	6.2e-108	4.5e-109	1.3e-26	2e-27	8.1e-133	6.8e-134
Bumetanide yn	1.5e-99	1.2e-100	1.6e-91	9.6e-93	8.8e-181	5.3e-182
Spironolactone yn	1.8e-89	1.5e-90	9.9e-51	9.6e-52	2.7e-138	2.1e-139
Thiazide diuretics category	2.2e-89	2e-90	1.1e-40	1.2e-41	3e-113	3.1e-114
NSAIDs category	1.9e-77	1.8e-78	1.6e-18	3.2e-19	1.2e-76	1.5e-77
Spironolactone dose	7.5e-76	7.7e-77	1.9e-48	2.1e-49	6e-122	5.4e-123
Trimethoprim yn	1e-69	1.1e-70	1.2e-36	1.5e-37	3e-104	3.3e-105
Serum Sodium	8.8e-63	1e-63	1.8e-63	1.2e-64	2.8e-117	2.7e-118
SBP	1.8e-62	2.1e-63	5.6e-25	9.1e-26	2.4e-86	2.9e-87
Days since diagnosis diabetes	3.5e-55	4.4e-56	2.3e-34	3e-35	6.9e-88	7.8e-89
Trimethoprim dose	3.5e-42	4.7e-43	9.9e-51	1e-51	8.1e-80	1e-80
PP	2e-35	2.8e-36	7.8e-07	2.1e-07	3.4e-40	5.5e-41
BMI	2.4e-34	3.5e-35	2.5e-05	7.3e-06	6e-37	1e-37
ACEI category	2.2e-32	3.4e-33	5e-27	7.4e-28	6.6e-43	9.5e-44
Bumetanide dose	2.9e-32	4.6e-33	1e-31	1.4e-32	1.4e-59	1.9e-60
Metolazone yn	2.4e-29	4e-30	9.1e-15	2.2e-15	5.7e-42	8.5e-43
Furosemide dose	7.3e-23	1.2e-23	0.0059	0.0025	1e-23	2.1e-24
DBP	2.1e-22	3.7e-23	5.5e-22	9.3e-23	5.6e-41	8.7e-42
Furosemide yn	5.7e-22	1e-22	0.011	0.005	2.5e-22	5.1e-23

[1] The following covariates were omitted from the table due to not having sufficient data to build a regression model: Xipamide yn; Xipamide dose; Sulindac yn; Sulindac dose; Penicillamine yn; Penicillamine dose; Flurbiprofen yn; Flurbiprofen dose; Fenbufen yn; Fenbufen dose; Amiloride hydrochloride yn; Amiloride hydrochloride dose; Aliskiren yn; Aliskiren dose; Acemetacin yn; Acemetacin dose; Aceclofenac yn; Aceclofenac dose.

Variable	BH corrected p value training set	P value training set	BH corrected p value test set	p value test set	BH corrected p value whole SIR	p value whole SIR
MCV	1e-21	1.9e-22	1.2e-09	2.9e-10	2.2e-30	3.9e-31
Amiloride yn	8.4e-17	1.6e-17	0.16	0.098	4.5e-16	1e-16
Metolazone dose	1.5e-16	3e-17	1.2e-18	2.4e-19	2.3e-28	4.2e-29
Aciclovir yn	4.8e-15	9.9e-16	0.0059	0.0025	1.2e-09	3.6e-10
ARBs category	4.2e-14	9e-15	1.9e-20	3.4e-21	2e-24	3.8e-25
Days until death	6e-12	1.3e-12	1.9e-32	2.5e-33	1e-31	1.8e-32
Trandolapril dose	2.7e-11	6e-12	0.47	0.34	9.2e-11	2.5e-11
Lisinopril yn	1.1e-10	2.4e-11	0.00059	2e-04	1.2e-13	3e-14
Cyclopenthiazide yn	1.6e-10	3.9e-11			1.2e-10	3.4e-11
Cyclopenthiazide dose	1.6e-10	3.9e-11			1.2e-10	3.4e-11
Sulfamethoxazole yn	2.7e-09	6.8e-10	0.84	0.76	3.9e-08	1.3e-08
AF	4e-09	1e-09	3.7e-08	9.4e-09	1.4e-15	3.3e-16
Anaemia	9e-09	2.3e-09	0.7	0.6	2.6e-06	9.9e-07
Hydrochlorthiazide dose	1.3e-08	3.4e-09	0.0056	0.0023	1.1e-10	2.9e-11
Mefenamic acid yn	3.5e-08	9.8e-09			2.5e-08	8.5e-09
Mefenamic acid dose	3.5e-08	9.8e-09			2.5e-08	8.5e-09
Candesartan dose	7.5e-08	2.1e-08	3.3e-19	6.3e-20	3.5e-22	7.4e-23
Piroxicam yn	8e-08	2.4e-08	0.0038	0.0014	1.2e-08	3.8e-09
Piroxicam dose	8e-08	2.4e-08	0.0038	0.0014	1.2e-08	3.8e-09
Smoker	1.2e-07	3.7e-08	9e-05	2.9e-05	3.1e-11	8.1e-12
HTN	2.1e-07	6.6e-08	0.07	0.04	3.9e-08	1.4e-08
Haemoglobin	4.9e-07	1.6e-07	0.97	0.92	2.4e-05	9.8e-06
Telmisartan dose	5.8e-07	1.9e-07	0.49	0.37	1.7e-06	6e-07
Hydrochlorthiazide yn	6.6e-07	2.2e-07	0.013	0.006	1.5e-08	4.8e-09
Candesartan yn	8.4e-07	2.8e-07	7.8e-17	1.7e-17	3.6e-19	7.8e-20
Trandolapril yn	2.7e-06	9.3e-07	0.47	0.34	2.4e-06	8.8e-07
Amiloride dose	3.9e-06	1.4e-06	0.7	0.6	1.6e-05	6.1e-06
Demeclocycline dose	5.1e-06	1.8e-06	0.036	0.019	0.68	0.57
Ramipril yn	7.1e-06	2.6e-06	7.1e-05	2.3e-05	1.7e-09	5.2e-10
Sulfamethoxazole dose	1.6e-05	5.8e-06	0.84	0.76	3.3e-05	1.3e-05
Diclofenac dose	3e-05	1.1e-05	0.54	0.42	0.0027	0.0013
IHD	3.2e-05	1.2e-05	0.026	0.013	1.4e-06	5.1e-07
Telmisartan yn	4.2e-05	1.6e-05	0.47	0.32	3.5e-05	1.4e-05
Ketoprofen yn	9.4e-05	3.7e-05			8.2e-05	3.5e-05

Variable	BH corrected p value training set	P value training set	BH corrected p value test set	p value test set	BH corrected p value whole SIR	p value whole SIR
Ketoprofen dose	9.4e-05	3.7e-05			8.2e-05	3.5e-05
Days since diagnosis AF	0.00014	5.6e-05	0.02	0.01	4.1e-06	1.6e-06
Valsartan dose	0.00032	0.00013	0.22	0.14	3e-04	0.00013
Quinapril yn	0.00035	0.00015	0.0086	0.0038	0.72	0.62
Quinapril dose	0.00035	0.00015	0.0047	0.0018	0.41	0.31
Diclofenac yn	0.00035	0.00015	0.7	0.6	0.011	0.0057
Demeclocycline yn	7e-04	0.00031	0.0086	0.0039	0.66	0.54
PVD	0.0021	0.00092	4.2e-16	9.8e-17	3.7e-13	9.2e-14
Aciclovir dose	0.0038	0.0017	0.0078	0.0034	0.12	0.072
Fosinopril yn	0.004	0.0018	0.98	0.97	0.0048	0.0024
Ramipril dose	0.0041	0.0019	0.45	0.31	0.0031	0.0015
Lisinopril dose	0.0079	0.0037	0.47	0.34	0.0059	0.003
Celecoxib yn	0.0082	0.0039	5.2e-05	1.6e-05	2.3e-06	8.5e-07
Immunosuppressants category	0.012	0.0059	1.6e-17	3.4e-18	4.3e-15	1e-15
Fosinopril dose	0.016	0.0078	0.98	0.97	0.016	0.0089
Chlortalidone dose	0.021	0.01	0.005	0.002	0.00029	0.00012
Practice ID	0.022	0.011	0.18	0.11	0.33	0.23
Valsartan yn	0.025	0.013	0.038	0.021	0.0016	0.00072
Indapamide yn	0.025	0.013	0.017	0.008	0.00078	0.00035
Bendroflumethiazide dose	0.04	0.02	9.1e-07	2.5e-07	2.8e-06	1.1e-06
Chlortalidone yn	0.054	0.028	0.005	0.002	0.0025	0.0012
Rifampicin dose	0.055	0.029	0.23	0.15	0.018	0.01
Mycophenolic acid yn	0.061	0.033	0.015	0.0073	0.0039	0.0019
Methotrexate yn	0.068	0.037	0.063	0.035	0.006	0.0031
Perindopril yn	0.073	0.04	0.49	0.36	0.043	0.025
Mycophenolic acid dose	0.073	0.04	0.018	0.0086	0.0028	0.0013
Verapamil dose	0.099	0.055	0.042	0.023	0.57	0.45
Losartan dose	0.12	0.065	0.39	0.25	0.46	0.36
Irbesartan yn	0.12	0.068	0.94	0.87	0.22	0.14
Perindopril dose	0.13	0.075	0.0097	0.0044	0.0066	0.0034
Indapamide dose	0.13	0.074	0.031	0.016	0.0076	0.004
Amphotericin yn	0.16	0.093	0.61	0.47	0.12	0.074
Verapamil yn	0.17	0.1	0.018	0.0092	0.011	0.0061
Etoricoxib dose	0.18	0.11	0.058	0.032	0.23	0.15

Variable	BH corrected p value training set	P value training set	BH corrected p value test set	p value test set	BH corrected p value whole SIR	p value whole SIR
Losartan yn	0.19	0.12	0.49	0.36	0.62	0.5
Meloxicam yn	0.21	0.13	0.97	0.93	0.24	0.16
Meloxicam dose	0.21	0.13	0.97	0.93	0.24	0.16
Irbesartan dose	0.22	0.14	0.96	0.9	0.34	0.24
Diabetes	0.22	0.14	0.85	0.78	0.36	0.27
Bosentan yn	0.22	0.14			0.21	0.14
Bosentan dose	0.22	0.14			0.21	0.14
Lymecycline yn	0.24	0.16			0.24	0.16
Lymecycline dose	0.24	0.16			0.24	0.16
Ibuprofen dose	0.28	0.18	0.98	0.98	0.34	0.24
Amphotericin dose	0.32	0.21	0.61	0.47	0.26	0.17
Torasemide dose	0.36	0.24	0.64	0.52	0.36	0.26
Aliskiren hemifumarate yn	0.38	0.26			0.36	0.26
Aliskiren hemifumarate dose	0.38	0.26			0.36	0.26
Ciclosporin dose	0.46	0.32	2.6e-17	5.7e-18	3.9e-12	1e-12
Celecoxib dose	0.46	0.32	5.2e-05	1.6e-05	0.00041	0.00018
Torasemide yn	0.5	0.35	0.64	0.52	0.53	0.42
Ciclosporin yn	0.5	0.35	2.9e-21	5.1e-22	6.2e-17	1.4e-17
Rifampicin yn	0.51	0.37	0.094	0.054	0.11	0.063
Naproxen yn	0.51	0.37	0.97	0.93	0.57	0.45
IMD Decile 2010	0.51	0.36	0.49	0.37	0.26	0.18
Naproxen dose	0.57	0.42	0.65	0.53	0.41	0.31
Ciprofloxacilin yn	0.58	0.43	0.5	0.38	0.35	0.25
Days since diagnosis PVD	0.63	0.47	0.0038	0.0014	0.033	0.019
Etoricoxib yn	0.65	0.49	0.034	0.018	0.66	0.55
Enalapril yn	0.66	0.5	0.82	0.72	0.57	0.46
Captopril yn	0.67	0.51	0.97	0.94	0.66	0.54
Nabumetone dose	0.68	0.53	0.0028	0.00098	0.16	0.096
Olmesartan yn	0.7	0.54	0.65	0.55	0.83	0.76
Doxycycline dose	0.71	0.55	0.34	0.22	0.41	0.3
Ibuprofen yn	0.73	0.59	0.43	0.29	0.41	0.31
Etodolac yn	0.73	0.59	0.13	0.077	0.83	0.76
Etodolac dose	0.73	0.59	0.13	0.077	0.61	0.49
Captopril dose	0.73	0.58	0.97	0.94	0.68	0.58

Variable	BH corrected p value training set	P value training set	BH corrected p value test set	p value test set	BH corrected p value whole SIR	p value whole SIR
Age	0.73	0.58	5.2e-05	1.6e-05	0.011	0.006
Nabumetone yn	0.74	0.62	0.0028	0.00098	0.077	0.046
Minocycline yn	0.74	0.63			0.72	0.63
Minocycline dose	0.74	0.63			0.72	0.63
Ethnicity	0.74	0.6	0.61	0.48	0.9	0.86
Days since diagnosis IHD	0.74	0.62	0.41	0.27	0.42	0.32
Olmesartan dose	0.75	0.64	0.65	0.55	0.69	0.59
Ciprofloxacilin dose	0.75	0.64	0.22	0.14	0.34	0.24
Lithium salts yn	0.76	0.65	0.37	0.24	0.95	0.92
Methotrexate dose	0.78	0.67	0.13	0.073	0.21	0.14
Tetracycline yn	0.82	0.72	0.93	0.86	0.89	0.84
Bendroflumethiazide yn	0.82	0.72	9.1e-07	2.5e-07	0.0016	0.00076
Lithium salts dose	0.83	0.73	0.45	0.31	0.93	0.89
Tacrolimus yn	0.86	0.79			0.85	0.79
Tacrolimus dose	0.86	0.79			0.85	0.79
Indometacin dose	0.86	0.78	0.62	0.5	0.99	0.97
Eprosartan yn	0.86	0.8	0.47	0.33	0.84	0.78
Eplerenone yn	0.86	0.78	5.8e-06	1.7e-06	0.027	0.016
Eplerenone dose	0.86	0.77	5.7e-07	1.5e-07	0.017	0.0093
Sodium aurothiomalate yn	0.87	0.82			0.86	0.82
Sodium aurothiomalate dose	0.87	0.82			0.86	0.82
Enalapril dose	0.87	0.82	0.43	0.29	0.57	0.46
Other nephrotoxins category	0.9	0.85	0.7	0.59	0.95	0.92
Indometacin yn	0.92	0.88	0.62	0.5	0.81	0.71
Doxycycline yn	0.94	0.9	0.25	0.16	0.68	0.57
Eprosartan dose	0.97	0.94	0.49	0.36	0.83	0.76
Triamterene yn	1	1	0.005	0.002	0.009	0.0048
Triamterene dose	1	1	0.005	0.002	0.0056	0.0028
Tetracycline dose	1	0.99	0.79	0.69	0.83	0.74
Imidapril yn	1	0.98			0.99	0.98
Imidapril dose	1	0.98			0.99	0.98
Gentamicin yn			0.84	0.76	0.83	0.76
Gentamicin dose			0.84	0.76	0.83	0.76

As discussed previously, the smaller the p-value, the greater the correlation of the feature with creatinine over time within the confines and assumptions of linear mixed regression. This is because a smaller p-value indicates a greater performance of the feature model compared to the null model without the selected covariate. In this case, we took the BH-adjusted $p<0.05$ to be within the range of significance.

The linear regression values have also been shown for both the test subset and the whole dataset. It is important to note that the p-values have merit in relation to each other only within-subset. Since sample sizes are different between datasets, we cannot compare between-subset p-values.

For this analysis, medication data was separated into 3 distinct types of variables. The overall drug category variable was labelled with the suffix 'category', and consisted of a binary variable indicating whether the drug was present in the prescription data at the time of the creatinine measurement. The named individual drugs comprised the other two types of variable. One binary variable indicated whether the drug was present at any dose, with the suffix 'yn', and one categorical variable indicated the dose of the drug prescribed, which had the suffix 'dose'. Therefore, if a 'dose' variable for a named medication was correlated, it could be said to have dose-related correlation as well as whether it was present in and of itself. If there was no dose related correlation but a positive binary variable significance, then the drug could be said to have correlation with renal function independent of dose prescribed.

4.5.1.1 Biochemical correlates

Biochemical covariates that strongly correlated to creatinine included potassium, serum urea, albumin, sodium, MCV, and haemoglobin. The most highly correlated

variables were urea and potassium, and this finding was consistent for each subset. A surprisingly strong correlation was also found in serum albumin, being the third highest ranked biochemical marker. Serum sodium was also found to have significant correlation though not as high as albumin. Haemoglobin, although a strong correlate, did not show as much correlation as the MCV value. Furthermore, the presence of anaemia, (i.e. Hb value lower than the threshold for normal for that gender) was more correlative as a categorical variable than raw Hb value as a continuous one. There were no biochemical lab-based covariates that did not show significant correlation.

4.5.1.2 Clinical correlates

The clinical and bedside parameters significantly correlated with creatinine included blood pressure, pulse pressure, BMI, presence and exposure to atrial flutter, smoking status, PVD, ischaemic heart disease, and exposure time to diabetes. Of these, systolic blood pressure was the highest-ranking clinical correlate, with p-value less than both pulse pressure and diastolic blood pressure, as well as the binary variable of hypertension as a diagnosis. Exposure time with diabetes was the second highest clinical correlate. However, the presence of diabetes in and of itself was not, only the duration of time spent with the disease.

Clinical covariates which were not strongly correlated, apart from diabetes as discussed, included exposure time to PVD, age, ethnicity and exposure time to IHD. IMD was not correlated significantly in any subset, but, practice ID, which was used to separate out patients belonging to different GP practices, showed slight correlation with a p-value of 0.022 in the training dataset.

4.5.1.3 Heart failure medication correlates

All the heart failure medication 'category' variables were found to be significantly correlated to renal function. Loop diuretics as a whole were the third most correlated covariate, and had the lowest p-value among all drug categories. Aldosterone antagonists were also found to have a high correlation, ranking them 5th out of all covariates, and 3nd in terms of medication categories, followed by thiazide diuretics. ACE inhibitors were found to be correlated more so than ARBs, though not as highly as thiazide diuretics.

Loop diuretics

In terms of specific loop diuretics, bumetanide showed the highest correlation, followed by furosemide. Though both also showed a dose-related correlation, the strength of correlation of furosemide's dose category was higher than that of its binary category (i.e. whether it was present at any dose), indicating a greater dose-related effect. The remaining loop diuretic, torasemide, showed no correlation in any subset.

Aldosterone antagonists / potassium sparing diuretics

The lowest p-value within this category was spironolactone, followed by amiloride. In both cases, the strength of the binary variable of drug presence exceeded the correlation of the drug dose category. Those found not to be correlated included triamterene and eplerenone.

Thiazide and thiazide-like diuretics

Metolazone was the thiazide with the lowest p-value across all subsets, followed by cyclopenthiazide, and hydrochlorothiazide, all of which also had significant dose-

related correlations also. For metolazone, the binary category correlated greater than the dose; for cyclopenthiazide, both categories had the same value; and for hydrochlorothiazide, the dose showed greater correlation than the binary category.

The diuretics bendroflumethiazide, chlorthalidone and indapamide had higher p-values and showed mixed results. For bendroflumethiazide, only the dose category was significantly correlated. Likewise, for chlorthalidone, the dose category showed significance, however the binary category was not significant in the training subset. For indapamide, the reverse pattern is shown, with significant binary category, and poor correlation for the dose variable in the training data. There were not enough data points for xipamide for it to be fully assessed in this analysis.

ACE inhibitors

ACE inhibitors which showed strong correlation with renal function included trandolapril, lisinopril, ramipril, fosinopril and quinapril each of which had low p-values for their binary categories. In addition, trandolapril and quinapril showed significant dose-related effects. In contrast, Lisinopril, ramipril and fosinopril were correlated only with the binary variable and not in a dose-related manner. The ACE inhibitors elanopril, captropril and imidapril showed no significant correlation for either binary or dose variables.

ARBs

For ARBs, candesartan showed the greatest correlation in all subsets, as well as a dose-related effect that surpassed the binary variable. Telmisartan and valsartan showed

significant correlation in both binary and dose variables, though dose related effects had a lower p-value than the binary variable in both cases.

ARBs which showed poor correlation in both binary and dose variables included losartan, irbesartan, olmesartan, aliskiren and eprosartan.

4.5.1.4 Other medication correlates

Antimicrobials

The presence of anti-microbials, while low in frequency in the dataset showed a markedly low p-value where present, ranking 4th on the list of correlates, and the second highest ranking drug category. Trimethoprim was the highest ranking anti-microbial in the data, and it also showed strong correlation in a dose-dependent manner. This was followed by aciclovir, which showed good binary and dose related correlation. Sulfamethoxazole and demeclocycline, while lower ranked, also showed binary and dose-related correlation in the training set.

Poorly correlated antimicrobials included rifampicin tetracycline, doxycycline, amphotericin and ciprofloxacin, with high p-values for binary and dose variables. Furthermore, limecycline, minocycline and gentamicin, in addition to having no significant correlation, also had some insufficient data such that a regression model could not be produced in all subsets. Lastly, penicillamine had the least data and could not be analysed in any subset.

NSAIDs

The greatest correlators in the training data were diclofenac, mefenamic acid, piroxicam, and ketoprufen. However, for mefenamic acid and ketoprufen, there was

insufficient data in the test subset to analyse. Furthermore, all of these except diclofenac had the same p-value for both the dose-related and binary variables, which means that only a single dose was used in each case.

Mixed results were found for celecoxib, which was only correlated in its binary variable in the training data, and not in its dose-related variable. The NSAIDs that showed poor correlation in both binary and dose variables included nabumatone, ibuprofen, etoricoxib, naproxen, etodolac, indomethacin and meloxicam. There was not enough data to support the analysis of acemetacin, aceclofenac, fenbufen, fluribufen and sulindac.

Immunosuppressants and other nephrotoxins

There were no medications in this section which correlated in the training subset, via either binary or dose variable. The medications in this section included mycophenolic acid, methotrexate, lithium, sodium aurothiomalate and tacrolimus with the latter two drugs having had insufficient data to analyse in the test dataset.

4.6 Discussion

4.6.1 Limitations

4.6.1.1 Limitations of the database

Coding and misclassification

The entry of patients into this study depends on accurate coding by GPs. Patients may potentially be coded wrongly into a heart failure cohort by the GP, or vice versa. Patients with either heart failure or any of our other covariates of interest may be

wrongly placed under a different read code. This database-wide error rate is prevalent in a human-coded system and leads to a degree of inaccuracy within both the patient cohort selection and identification of subsequent risk factors. Inherent flaws in the data are not easily corrected, and it is important to recognise that this affects all the data in this study, and in large part, all clinical data obtained from primary care data is subject to this human error bias.

Medication information

Medication data is recorded as prescriptions issued in the GP system, and not by actual use of medication by the patient. Therefore, medication adherence cannot be clearly determined since the prescription may not have been used by the patient. Furthermore, we are unable to monitor exact timings of medication start/stop times. An assumption of adherence must be made for each patient for each prescription issued; however, this patient cohort is clinically complex with many co-morbidities and multiple medications. Reasons for non-adherence are multi-factorial and we cannot account for its presence within our cohort, which may lead to bias.[292] Our assumptions of start and stop times also make it difficult to adapt to complex medication regimes or self-dosing of medications like diuretics. Closer integration between pharmacy and GP data may be able to mitigate this in the future; however as an integrated system-wide problem, this is a major caveat when interpreting medication data currently.

Secondary care prescribing data

The lack of a true link between primary and secondary care prescribing data is an important limitation. This essentially means that any changes to diuretic medication

including initiation or cessation as a hospital inpatient would not be available as recorded data at the correct date. In this study, we assumed that changes from hospital would be continued or reciprocated by the GP; however, this may happen weeks to months from the initial inpatient prescription, if at all. A linked dataset may be able to capture this data, but as with the caveat above, more precise medication data is required on both fronts for this to be utilised effectively in the future.

Lack of secondary care data

As previously elaborated, SIR data sometimes captures data from hospital sources regarding patient clinical outcomes; however, the frequency of this and its consistency is variable. Furthermore, the extent of the data obtained is sparse, and it is not accurately time-stamped. These inconsistencies mean that the interspersed secondary data is of limited value. In addition, the dataset would miss out on patients that present solely to secondary care services such as hospital-based heart failure clinics, where there may be an unrecorded cohort of severely ill patients.

Bias towards frequent measurements

As the association study relied on the frequency of creatinine measurements to create comparisons between other variables, it may be the case that the associations are biased towards the patients who are at the lower end of renal decline. This is because, as shown in table 4.6, the patients with a higher stage of CKD had a higher frequency of measurement. Therefore the data will be richer in the patients with more marked renal dysfunction, and thus a bias may arise due to the disparity between over-testing this sicker population, and under-testing the more stable kidney function patients. This is

a limitation of studying a retrospective database, in that measurements are infrequent and down to clinical judgement, however it also speaks towards the lack of clinical guidance in this area, in that the measurement frequency for more stable patients was extremely variable.

4.6.1.2 Limitations of the study design

Generalisability

This study assumes that the analysis from this retrospective patient cohort can be generalised to the current population of heart failure patients in the UK. This assumption may be questionable for several reasons:

Firstly, this analysis captures a patient cohort with chronic heart failure who have presented to their GP. This produces a selection bias towards healthcare-seekers with heart failure, and may not capture sufficient data on the hidden cohort of patients suffering with heart failure without presenting to primary care. Furthermore, the results of this analysis may not be applicable to patients managed in secondary or tertiary care, or who present with acute heart failure.

Secondly, there may be historical differences between the patient cohort analysed and the current population. This difference exists in both the treatment of chronic heart failure and in the measurements used to record clinical outcome. Over time, the treatment trends and preferences for chronic heart failure have evolved, from late symptomatic treatment to early prevention and a greater reliance on implantable medical devices. In addition, the measures for assessment of renal function decline have changed over time. New methods of calculating eGFR and more accurate creatinine assays have been developed,[293] and monitoring practices have evolved

with them. A retrospective historical analysis of treatment and monitoring patterns may wrongly attribute them to current practices.

Insufficient outcome data

In a community setting, frequent creatinine or eGFR testing may not be considered necessary or practical by GPs, and we expected clinical practice to vary greatly with regard to monitoring renal function. This non-standardisation of testing is one of the precepts of this study, but it does pose an obstacle for predictive time analysis. The strength of the analysis relies on the frequency of measurement of biochemical markers for renal function in the selected dataset. Furthermore, infrequent data points relating to creatinine will reduce the accuracy of the predictive model that can be generated by machine learning, since we cannot check creatinine outcomes at fixed time intervals. This is likely a problem for any time-based predictive model, and we used creatinine, partly because it is one of the most frequently tested measures in primary care to allow for this.

Missing data

With the limitations of primary care clinical datasets involving a significant effect of missing data led to a substantial analytical challenge in terms of correcting for this missing data. It unfortunately led to compromising certain covariates that were deemed important to the outcome of renal decline such as urinary albumin, or to heart failure such as serum BNP. It may be that in this historic dataset, these tests were not as frequent as current practice and so efforts need to be made to create an effective

method of updating any predictive model with new information to minimise the bias from this missing data.

Causality

Observational data do not imply cause and effect in and of themselves. The association study may imply that there is an association, but further evidence is required in order to clarify the sequence of causality which leads to each outcome. This is a criticism of any regression analysis in that we may be discovering an effect of the outcome rather than the cause. For the goal of prediction, these effects may still be useful; however, in order to prevent the outcome, further detailed trials are required.

Likelihood ratio testing

The p-values obtained from the association study compare the likelihood ratios of a null model versus an active model which has each variable added on individually, to test for association with log(creatinine). The main benefit of the test is to determine how likely that an association exists between any given variable and log(creatinine). In this way, it is difficult to compare the p-values directly against each other as a measure of correlation in and of itself, and this may require further validation using R-squared values which is detailed more in the next chapter. However, it does provide a starting point for which variables are more likely to independently increase the goodness of fit of the overall model by their addition.

4.6.2 Summary of feature selection study

The purpose of this study was to create a comprehensive dataset of heart failure patients, weighing their clinical parameters over time and comparing them to renal function to derive determinants of renal health. This would then go on to inform future predictive models for renal decline, specific to heart failure patients. To this end, the raw data from Salford was extracted and processed to a standardised format such that each relevant clinical parameter and medication prescribed was identified and linked to creatinine over time. This format aided longitudinal trend analysis of renal function relating to each variable.

The cohort within the study window of 8.5 years was studied to gain insights into the characteristics of this retrospective chronic heart failure patient population. The data was then filtered for viable covariates to link to creatinine over time and correlations were assessed using linear mixed model regression. The results of this will lead on to our machine learning methods for predicting renal function over time, in order to generate personalised guidance for renal monitoring in heart failure.

4.6.3 Dataset generation

Manual processing of the raw data into a suitable format was the most time-intensive step of this method. The clinical data from primary care systems is largely unstructured and of little use in its raw state. Each step of processing discovered numerous errors and sources of bias that required efforts to minimise, such as the presence of duplicated data, and the assumptions that needed to be made for medication. While it may be that source-standardisation is unlikely to occur without a nation-wide shift in EHR practices, there may be novel methods to approaching this post-processing itself. Recent advances in natural language processing have shown success in isolating and

identifying individual clinical parameters from raw digital health records, which may be a boon to future studies requiring processing of unstructured data. [294-296]

4.6.4 The heart failure patient cohort

From the analysis of the patient cohort of heart failure patients, numerous notable observations can be made, many of which are well established in the literature, but some of which may be specific to the location and timing of this selected subgroup. Demographically, the cohort consists almost entirely of Caucasian patients, the majority of which come from very deprived areas, as evidenced by the average IMD decile of 3 (albeit a proxy measure of deprivation as it is based on GP practice location rather than patient postcode). It is important to view the observational findings of this population in context of these risk factors and with the knowledge that this is a chronic heart failure population, with an average age of 76, to fully distinguish this population from other patient groups.

The national average age of patients with heart failure matches the findings of this study, yet of note was the fact that the age of diagnosis differed between men and women, with men diagnosed on average 4.5 years before women (72.5 vs 77).[2] When we look at other risk factors for heart failure in order to explain this, we find a higher proportion of men diagnosed with ischaemic heart disease and a higher proportion of recorded smokers. On the other hand, rates of diabetes, atrial fibrillation, obesity, and end-stage renal failure remained comparable and rates of hypertension were even higher in the female group.[3] Recent observations of acute heart failure hospitalisations indicate there is a greater risk of all-cause mortality for patients with lower baseline SBP.[297, 298] This may be due to inability to increase stroke volume

to meet demand under stress. While this may go part-way to explaining a gender difference, the overall mortality was consistent between groups (25% vs 26.6%).

It is also important to consider the extreme variation in renal monitoring practices observed in this study. While the average interval time between tests recorded at 51 days, the SD value of 99 days means that the range for most of the monitoring fell within 8 months, a far cry from the average value of 7 weeks. There has been little evidence to compare this to, since there is no gold standard of monitoring by which to assess primary care practices against, and also due to the nature of renal function monitoring in that its needs and use vary on a case-by-case basis. This study shows that this practice requires more precise guidance, not only to advise clinical practice but also to create a baseline to compare against. As it were, the monitoring frequency increased with increasing CKD stage, as would be clinically expected, yet further investigation may be required as to which other covariates may prompt further GP investigation, to explore this area further.

While a majority of patients at one point in the study were diagnosed with hypertension, this was mostly due to a high systolic BP. Yet looking at the diastolic blood pressure shows a 40% rate of less than 60 mmHg. These contributed to a high rate of wide pulse pressure in these patients. While this is well documented as a finding in heart failure patients, it is more associated with an effect of increasing age in the western population likely due to worsening atherosclerosis. It is important to note that while the numerous co-morbidities have associations with heart failure as a disease process, many occur as a product of degenerative processes which become more common with age.[299, 300] While pulse pressure has, by and large, been thought of as a predictor for poor cardiovascular outcomes, recent studies suggest that a widened pulse pressure (>50) may in fact be protective in heart failure with reduced ejection

fraction.[301, 302] In this incident heart failure population, the rate of widened pulse pressure of 89% may suggest an active compensatory process that is promoting this potentially protective effect.

In observing how rate of co-morbidities in this study differed from average rates in heart failure patients across the UK, we compared our frequencies with a recently published population-based study, which looked at 93,074 incident heart failure patients from between 2002–2014. Conrad and colleagues[303] used CPRD data to screen 4 million patients for heart failure diagnosis and then analysed the incident population, creating a cohort much like our study, but from a wider area. The timings of both studies also overlapped, though it is worth noting that our study had a more recent cohort from between 2008 to 2016. Ethnicity was similar in both studies: 97% were Caucasians in the CPRD data compared to 98% in this study. However, in terms of IMD, the situation differed, as CPRD appeared to have a roughly even split between quintiles of around 20% each. The average age was comparable, but CPRD data had a more even split of gender proportions (49% female, versus SIR 45%). In terms of co-morbidities, rates of obesity (BMI > 30) were higher in SIR (43% vs 32%) but there were higher rates of missing data in CPRD (40% vs 0.7%), likely due to the fact that we calculated BMI manually, and so this may represent a database effect rather than a true population difference.

Perhaps the greatest difference was that shown in CKD rates; while CPRD recorded a rate of 24% in their population, in Salford the rate of CKD 3-5 was 53%, representing a major disparity. Rates of atrial fibrillation in both studies were equal at 40%. The rate of diabetes was slightly higher in SIR compared with CPRD (30% vs 22%). Hypertension had a lower frequency in this study (57% vs 67%), but in contrast, the rates of IHD were higher (59% vs 49%) in SIR over CPRD. These observations allow

for some significant insights between the two population groups; however it is important to consider that database comparisons such as this cannot account for the way each covariate has been processed and analysed, which means there is a hidden effect of the database processing that would bias any comparisons made. In addition, the study windows and follow up times differed in length which would contribute to an observed difference in disease frequency. To investigate this further, it may be a logical next step to apply this same method of database processing to CPRD data, within a similar study window to determine the true disparity, and what other covariates may be contributing to the increased renal decline in Salford compared to other populations.

4.6.5 Notable correlates with renal function

From the outcomes of the feature selection study, we now know that the greatest predictors for creatinine behaviour over time include the biochemical variables of serum urea and serum potassium. However, other interesting correlations have emerged from this data which may be an avenue for further research, for example, serum albumin, which is not normally assessed in renal decline. Clearly serum albumin can be low in nephrotic syndrome and protein-losing nephropathies which cause albuminuria.[304] It also plays a part in assessment of urinary ACR, one of the diagnostic criteria for CKD. The extremely high correlative value may suggest that it is a strong predictor by itself and should possibly be given more credence in renal assessment of CKD patients. Certainly, there is evidence to suggest that low albumin is a contributor to renal-related morbidity and mortality.[305, 306]

Another interesting correlate is that of exposure time to diabetes, but not the diagnosis of diabetes in itself. This suggests a time-dependent effect of diabetes on renal function that is mirrored across patient populations. While it is known that diabetic nephropathy is more common with increasing age, it may become more useful to determine the time of diagnosis of diabetes and how long patients have had the disease, in order to get a true sense of the renal impact of diabetes.[307]

Mean corpuscular volume is another covariate which has been overlooked with regard to renal decline. It is well known that a lack of EPO in CKD causes anaemia of chronic disease, but little regard has been put into the assessment of MCV. This is evidenced by the sparse literature regarding the topic. This is compounded by the fact that in this study, MCV correlation appeared to be greater than that of haemoglobin. A single study of 1439 patients investigated outcomes of different MCV values in patients with CKD and showed that a macrocytosis was linked to greater all-cause mortality.[308]

This study is rich with drug-related data regarding correlates with renal function. It is not surprising that loop diuretics were the most significant predictor among the drug classes. However, it is important to consider that less commonly prescribed diuretics such as xipamide and torasemide may have shown a lack of significance simply due to having sparse data on the drug, rather than a lack of effect on renal decline.

Further evidence towards this can be found in the results of gentamicin. This antibiotic has been well established to have severe acute renal effects, and this is widely observed in hospital settings.[309] However, in our study, it was shown to be non-correlative, and there was not enough data in the training set to build a regression model. It is likely that further data regarding exposure to gentamicin would reveal its nephrotoxic effects. Therefore, particularly for drugs that do not appear often in this database, their renal correlate is still very much an unknown.

Conversely, medications which are prescribed more commonly are more likely to show an effect or reveal their correlation with renal function more readily. The most significant antimicrobial correlate was shown to be trimethoprim. This is a commonly prescribed treatment for urinary tract infections which, in turn can be linked to renal decline. There is even evidence to suggest that trimethoprim's mechanism involves increasing serum creatinine, which may be independent from renal function.[310, 311] It is interesting to note that the rate of antimicrobial prescribing in female patients was greater than that of males (13% vs 9%) and this may relate to the fact that urinary tract infections (UTIs) are more common in females. Thus, it is difficult to attribute causality directly to trimethoprim as the renal effects may also be due to the underlying UTI.

Overall, while the study can suggest new links and associations between creatinine and other clinical and biochemical markers, including some medications, it cannot elude to the nature of this association. At most it can open new paths for potential research into renal decline to better understand its process in this complex patient population.

4.6.6 Utilising the output of the correlation study for prediction

Now that a set of predictive variables has been collected, the aim was to use these correlative findings as a starting point for creating a predictive model for renal function over time. Starting with the variables most highly correlated, the analysed covariates were assessed and considered for use in generating a machine-learning model with the greatest predictive accuracy.

CHAPTER 5

GENERATING A PREDICTIVE MODEL OF RENAL FUNCTION USING MACHINE LEARNING

CHAPTER 5: GENERATING A PREDICTIVE MODEL OF RENAL FUNCTION USING MACHINE LEARNING

5.1 Introduction

This chapter focuses on using the results in chapter 4 to create a predictive algorithm based on creatinine measurements, and hence renal function. In doing so, it will provide a platform from which to design a guideline around renal monitoring that can adapt to each patient's individual characteristics, making it truly personalised.

5.1.1 Machine learning

Machine learning is an umbrella term for a range of data science methodologies that self-adapt to a given task. In principle, this involves an algorithm which is trained towards reaching a certain outcome, be it classifying data into categories (classification), predicting a continuous variable (regression) such as creatinine, or identification of a substructure in the data (clustering, unsupervised learning). The algorithm is provided with only a dataset and an end-point and is tasked to adapt its parameters and coefficients to reach the end-point in the most efficient manner. The input data is known as the 'training dataset' and the finalised algorithm is tested on an independent 'test dataset' for validation.

As an example of classification, CKD patients are divided into stages 3, 4, or 5 depending on their calculated eGFR level (<60, <30, <15ml/min, respectively). Normally we have eGFR available and can simply categorise patients in this way. However, machine learning allows us to estimate this classification even without eGFR, as long as we train the algorithm with a dataset that has the known CKD stage. The algorithm will 'learn' from this training data, by making associations between covariates and similarities between patients who have the same stage, so that when exposed to new data that has the stage 'hidden' it can predict the correct class based on its observations of other covariates, without knowing eGFR. This is known as

‘supervised learning’ since the ‘outcome’ of CKD stage is defined clearly and known in the training dataset.[312]

‘Unsupervised learning’ is a type of machine learning technique where the outcome class is not known, and the machine is tasked to make its own classifications based on similarities it observes, iteratively, from the data. This can create complex and grounded algorithms that are entirely based on the quality of training data provided, but ones that can also find links and associations that would be difficult or impossible to otherwise identify. The resulting machine-learning based clustering would create a new set of classes for kidney disease that may be more apt for explaining the data given, or could theoretically be better than the current standard.[313]

5.1.2 Statistical techniques vs machine learning

For the task of predictive modelling, this means that a machine learning technique is able to analyse large sets of data and makes its own coefficients and transformation for each variable in order to determine the outcome. This is in contrast to traditional statistical regression such as the linear mixed model used in the previous chapter, which uses multiple assumptions (each of which impacts bias to a greater extent) in order to determine the correlation of different variables to creatinine. The resulting statistical model from linear regression can be used for prediction. However, those assumptions are still in place, meaning that non-linear relationships cannot as readily be evaluated, and each variable is seen as being independent and separate from each other, which we know is not the case. Machine learning is potentially unrestricted by these assumptions and will find links and associations between covariates of the same patient, linearly and non-linearly. For training a predictive model, we set the task of

the algorithm to minimise error in the prediction, so that the machine learning process will actively change to adapt to the highest predictive coefficient of each covariate to estimate the output (of log creatinine in this case).

It can be argued therefore that for clinical data with many multicollinearities between variables, machine learning algorithms may be more suited for adaptive predictions. While statistical methods are viable and have been used in practice for risk assessments of patients with co-morbidities, they are limited in that they paint all patients with the same brush and are unsuited for a guideline which requires flexibility around each patient. They are also likely to be less suited for predicting an outcome that is not yet known. Machine learning allows us to both create custom categories of patients at risk and create predictions about patient characteristics in the future, and we can use this information to determine customised clinical rulesets for each patient individually.

5.1.3 Drawbacks of machine learning

One of the common drawbacks of machine learning in clinical use is that the algorithm learning process cannot be easily replicated. The same data set through the same methods can be analysed statistically to obtain the same regression line each time, but this does not apply to machine learning, where the process is emergent and may have a different outcome each time. Furthermore, the regressor in a statistical method can be easily explained and examined in its own right to evaluate its use in certain situations. However, a machine learning algorithm in its classical form is unique, does not lend itself well to theoretical evaluation, and is sometimes purely imperceptible, as is the case with 'neural networks'.[314] This black box approach to prediction means that there are a large number of unknowns pertaining to the algorithms

generated by machine learning, and the only way their performance can be validated is on test datasets. Further validation may seek to strengthen the trust placed on a specific algorithm, but it says nothing of its biases and over-/underestimates in covariates since each coefficient is not under direct human control. Apart from being clinically risky, this makes it difficult or almost impossible to standardise techniques over a large scale, without using the exact same algorithm. Yet, since the algorithm, training data, and method, are all linked together, if an issue arises with the algorithm generated, then the entire machine learning experiment needs to be re-trained from the beginning, since we cannot easily untangle the algorithm from the data and just adjust the coefficients manually. It therefore makes any resulting algorithm difficult to interpret, and requires both training and test data as well as its generation method itself to be assessed for reliability. This is in contrast to statistically generated regressions that can clearly delineate the relationships between certain covariates and the outcome and can thus lead to further investigation of each coefficient. This is part of the reason why statistical methods are more suited for looking at relationships between covariates in the present and how they interact, rather than looking at predictive outputs.[313]

Another drawback of machine learning algorithms is that, since the entirety of their optimisation cycle is dependent on the training data, they are highly susceptible to a specific type of bias known as ‘overfitting’. This refers to when the algorithm is over-adapted to the training data such that applying it to a different dataset will produce errors disproportionate to that of the training subset. In other words, the machine learning process has taken the characteristics unique to the training dataset into its decision rules and then expanded that to a greater extent than is required, which makes it less generalisable, since it produces errors when working with any dataset other than

the one it was trained on. Overfitting is part of the reason why the test data validation is so important, to confirm the extent of this bias.[315]

Despite these caveats in machine learning, the advantages in terms of predictive ability and flexibility of these techniques warrants investigation in clinical practice, and hence our design to facilitate its use in a predictive tool for renal function. In this study we have leveraged the correlative benefits of statistical analysis with the predictive potential of machine learning to create an accurate model.

5.1.4 Examples in clinical care

In medicine, machine learning is often used to enhance the applications of diagnoses, or for prediction of clinical variables and outcomes. These tools are already being trialled in clinical practice. For example, Wang and colleagues[316] have developed a clinical prediction tool using artificial neural networks, which can predict fasting glucose using the covariates of uric acid, urea, alanine transaminase, total protein and BMI. Machine learning models have also been utilised in high volume data areas of clinical practice such as ICU, in order to predict length of stay for patients.[317] Certain algorithms have even been designed to predict the rate of adverse drug reactions in patients using their own genetic data.[318]

It is also important to acknowledge the advances made by deep learning methods on the analysis of clinical imaging. Ophthalmology, radiology and other specialties which rely heavily on interpretation of images and scans have benefitted greatly from this approach. Several methods and techniques have been shown to have a wide array of clinical benefits to interpreting retinal images, for example to identify retinal detachment,[319] haemorrhage,[320] and overall vasculature of the retina,[321]

making it an indispensable tool for the future. For radiology, machine learning tools have helped assist in improving the accuracy and efficiency of diagnosis and treatment of a wide array of conditions, and to a standard comparable or even surpassing that of human interpretation.[322, 323] As mentioned in the previous chapter, several applications that are also being trialled are the use of language processing for navigating large sets of electronic health records.[324] Some of the uses for this include identifying key risk factors or diagnoses from unstructured text,[325, 326] identifying patients lost to follow up,[327] or scanning social media to look for public health risks.[328] Many of these uses involve classification outcomes using free text as an input, yet there are also uses to help with processing large datasets such as in this study into usable formats for clinical trials and population studies,[329] which is an exciting prospect for the use of big data in medical research.

5.1.5 Machine learning techniques

To identify the optimal methodology for using our dataset to predict creatinine, various machine learning methods were evaluated in relation to our study aims.

5.1.5.1 Artificial neural networks (ANN)

Artificial neural networks are a family of statistical learning algorithms that are used to estimate or approximate functions that can depend on many inputs that are generally unknown. It is a type of unsupervised machine-learning, and is sometimes thought of as ‘deep learning’, since it involves much more internal/automated regulation than most machine learning tools. Rather than training a single computational process towards an outcome, it involves the building of multiple layers of computation, each

layer has several nodes and each node makes its own individual observations and undergoes a separate learning process. The outputs from each layer connect to other layers, and are then combined together to achieve an output based on a multitude of underlying computational structures. ANN, is so called since it is has analogues to human neural networks, with multiple neurons activating and tasked with specific areas all to come to a complex decision.[330] These networks have been used for a variety of medical applications including the aforementioned radiography interpretation algorithms, each node looking at a distinct input, or a separate part of the radiograph, to reach a diagnosis.[331] The exact number of nodes and layers differs in each ANN, and this is not fixed. Figure 5.1 below shows an example of a multi-layered ANN with a single hidden layer.

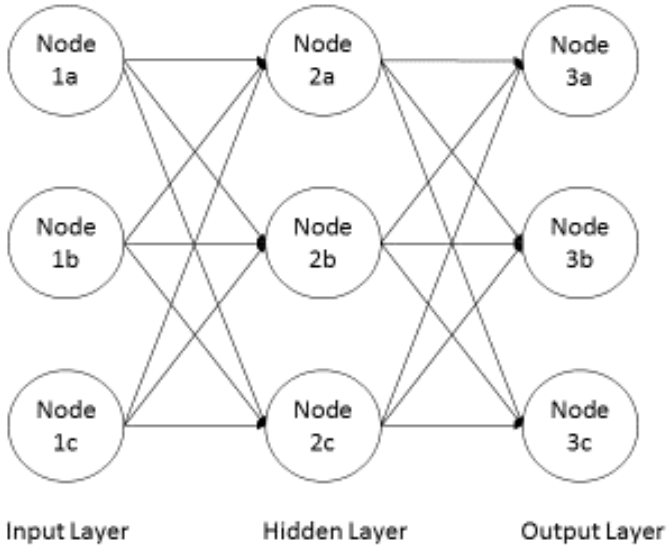

Figure 5.1 Diagrammatic representation of a multi-layered neural network[332]

In our study, we considered creating a neural network that can process all the variables available in our dataset, and outputting a prediction of creatinine at a fixed time point in the future. The advantages of this method are that it can input the multitudes of

covariates and reach an output using all the clinical data available in an intelligent manner.

The drawbacks are that ANNs are not traditionally well suited for handling longitudinal data, but are better able to deal with information in a snapshot.[333] To accommodate this, we would have needed to calculate the trajectory of change as a separate variable to allow it to be input into the network. Secondly, rather than regression, these networks are more suited to classification tasks, such as defining risk categories, rather than actual creatinine value. Furthermore, the inputs to each 'node' require them to be separate and independent to each other, since multicollinearities between inputs will likely create bias within the algorithm. This is difficult in a clinical dataset to design and would necessitate the creation of 'amalgam' variables which combine several other variables into one 'score' in order to compress together data with co-linearities, all to satisfy these criteria. This was attempted in order to determine feasibility of this method for large clinical datasets (Figure 5.2).

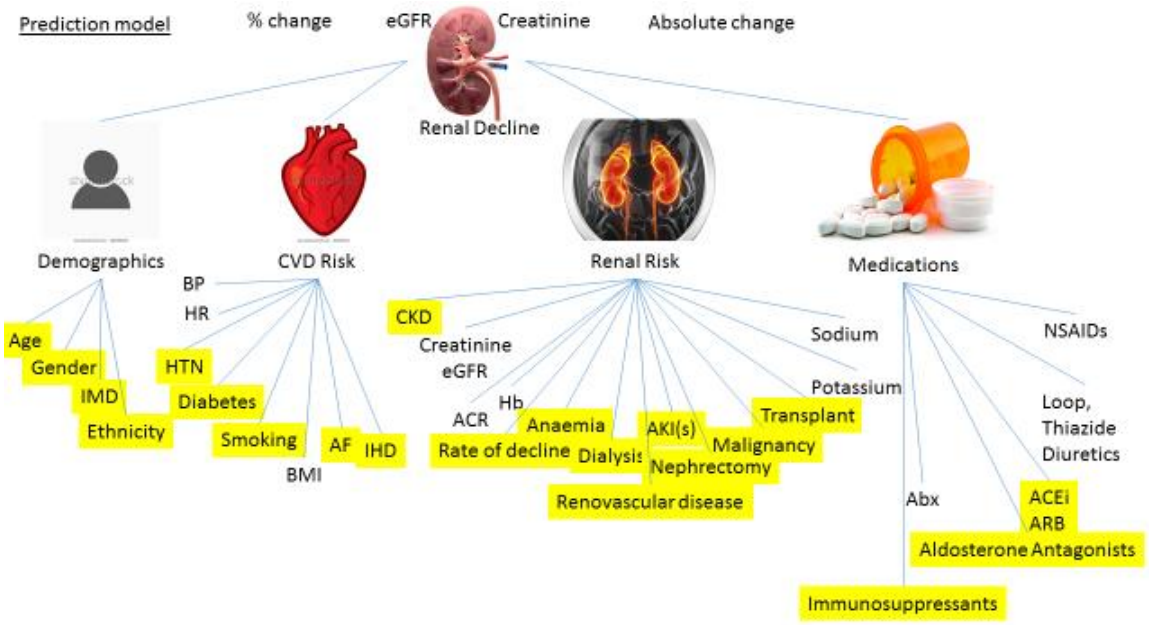

Figure 5.2 Diagram representing theoretical neural network structure in predicting renal function over time

Figure 5.2 shows a preliminary model used to form the following 4 amalgamated clinical groups using separate but linked covariates, in order to accommodate the requirements of the artificial neural network. However, the complexity as well as the lack of precedent or validation for creating these groups proved to be unfeasible within the confines of this study. Therefore, the drawbacks of this ANN process were too great to overcome within the timespan of this project. Furthermore, the resulting guideline generated would be seen as too much of a black box with little clinical basis to be interpreted reliably by the clinicians that would eventually use the algorithm to make decisions. This may yet be a possible future research avenue, but for our current purpose, it was not suited as the best method to create a predictive model.

5.1.5.2 Clustering

In researching previous attempts of longitudinal prediction, clustering methodologies emerged as a promising concept. This method involves using machine learning to 'learn' the patterns of change over time, and then group together those with similar patterns. In our study the application would be to group together patients that have similar patterns of renal change in response to their clinical variables. These clusters can then be identified by the risk of future renal decline and patients can be classified into them, thus creating a measure of risk.

This is a type of unsupervised learning[334] as described previously where the algorithm is left to decide the optimal grouping of the patients within the dataset.

The advantage of clustering, compared to other methods of predictive analysis, is that it does not require patients to be tested at specific time intervals.[335] This is because

the merging of multiple patients' data together into one group can be used to strengthen each specific category, making a well-defined cluster even if some patients have infrequent or few measurements. Certainly, it was shown in the previous chapter that there is high variability in monitoring practice in our dataset, making standardised timelines difficult to map to each patient individually. Clustering can therefore be used to mitigate this inherent characteristic in our retrospective primary care data.[336] There was also precedent in using this technique to make sense of unstructured retrospective data for patients to assess their risk of CKD. Figure 5.3 demonstrates this key insight, which justifies the use of clustering methodologies in our dataset. Huopaniemi and colleagues[336] used retrospective longitudinal hospital data over 16 years and clustered the eGFR trajectories of 10,539 patients. This resulted in 9 discrete clusters, each made up of large groups of patients with similar eGFR trajectories over time. Each patient individually had varying degrees of follow up and missing data, but each of the clusters was well defined. The change in eGFR over time could then be quantified, creating different risk categories for CKD based on each cluster.

Working within the confines of the SIR dataset, which shares similar characteristics, this method showed promising potential in explaining our data in a meaningful manner. Patients with similar creatinine trends over time would be grouped together into clusters in a similar way. The cluster patterns generated from these groups of patients could then be used to map out the likely trajectories of new patients that fit the cluster, predicting renal change over time.

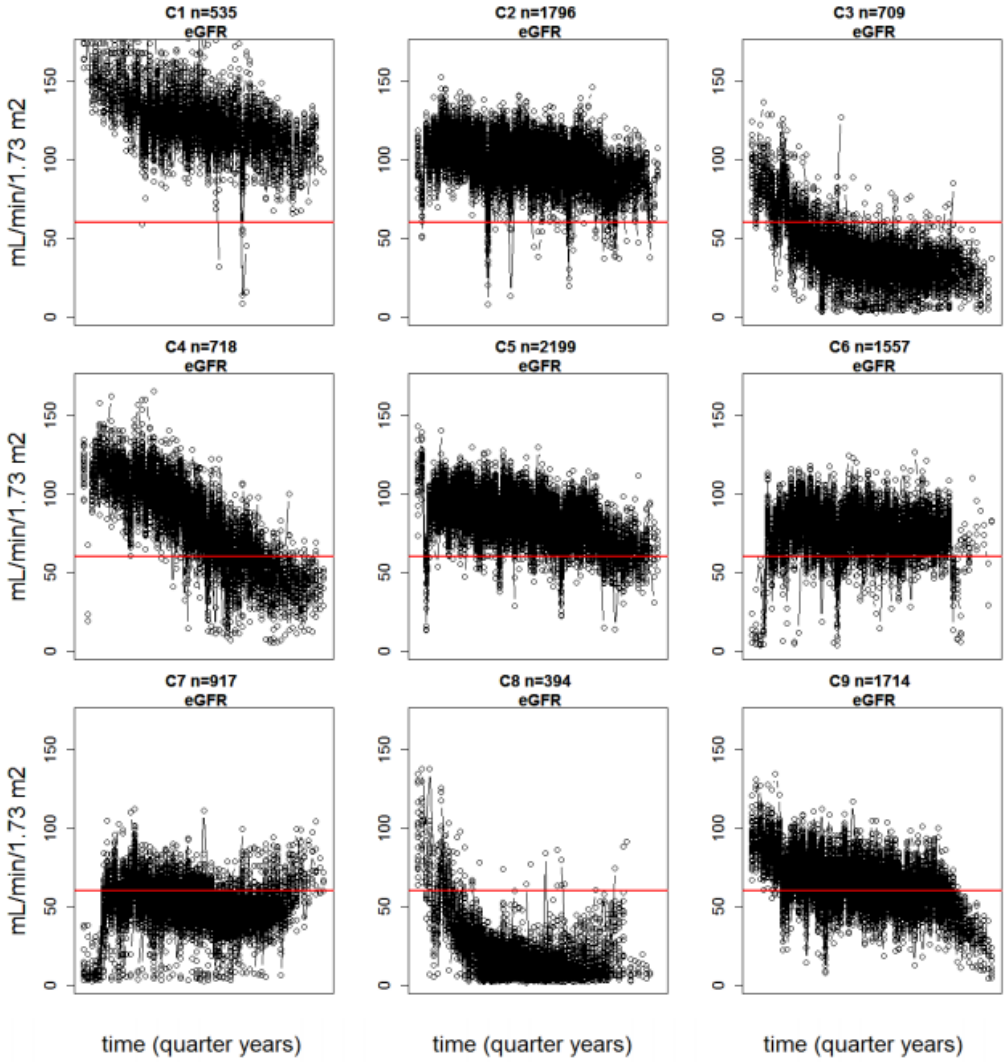

Figure 5.3 Clustering of eGFR longitudinal trends in 10,539 patients over 16 years as published by Huopaniemi et al.[336] n= number of patients per cluster, C = cluster index

5.1.6 Clustering mechanism

The most common tasked format of the clustering process follows an expectation-maximisation (EM) algorithm. Each data point is assigned to a random cluster initially, then the cluster assignments are optimised iteratively over the course of this process by alternating between the expectation and maximisation phases. In the expectation phase, the centroid of each cluster is calculated. The centroid of a cluster may be defined in several different ways depending upon the specific clustering type used (e.g. distance-based or shape-based). Either way, this becomes a value by which other

observations are compared against. In the maximisation phase, each observation is re-assigned to the cluster whose centroid it is closest to. Again ‘closeness’ can be re-defined depending on the characteristics of the clustering method employed.

Repeating these phases causes the clusters to begin to converge into more distinct and cohesive entities. The process continues until no further changes occur to cluster assignments, i.e. the probabilities of each observation belonging to each cluster have been maximised. This is known as ‘hill-climbing’ since the coefficients become more and more optimised over time with each recurring iteration until they reach a peak ‘the top of the hill’.

5.1.7 Model-based clustering

As previously mentioned, the ‘closeness’ of each centroid can be evaluated by different longitudinal clustering methods. Distance-based clustering looks at the longitudinal trend line of each patient over time and creates a mean trend-line for each cluster, then groups together the patients nearest to it in a plot of the variable over time. This means that patients with high creatinine mean trend lines are grouped together, and low creatinine mean lines are grouped together similarly, without regard to variability of the line. Shape-based clustering looks at the shape of the trend line for each patient and creates a mean shape, which is then compared to each patient for grouping. This allows variability to be considered regardless of starting creatinine, however, it is heavily reliant on frequency of measurement.

In contrast to distance and shape, model-based clustering looks at the relationship between the dependent and independent variables in a data series. Its expectation phase creates a model of how these variables correlate to each other, and the maximisation

phase assigns observations based on similarity to the generated models. In terms of this study, it creates clusters based around the relationship between log(creatinine) and the other selected features, and then assigns longitudinal patient data based on how closely they fit these models, optimising and re-evaluating the models as it goes along. This means that each cluster will contain groups of patients whose renal function over time act in the same way in response to the other related covariates. This bypasses the limitations of both distance and shape-based clustering for our dataset. Since patients are clustered in a correlation-based manner, the number of measurements has less of an impact than shape-based clustering. Furthermore, patients with high variance will be clustered together regardless of starting creatinine. This method also lines up well with our feature selection step, which involved a linear mixed model to select the required covariates, so a clustering algorithm drawing from the outputs of this would be synergistic.

As far as a platform for predictive analysis, clusters based on models would be ideal, as each cluster can create a prediction in its own right and also inform on the properties of renal change for each patient within the cluster. The model derived for each cluster can be extrapolated for prediction, as well as allowing us to categorise each cluster in terms of risk.

5.1.8 Drawbacks of clustering methodology

While this clustering methodology is well suited for analysing longitudinal data as has been discussed, it is nevertheless extremely computationally taxing. While our initial goal was to rely on machine learning as the main solution for creating the predictive model, certain accommodations needed to be made for the clustering methodology to

work best. Among these, the number of input variables needed to be minimised as much as possible, since the computation time increases exponentially with each added covariate. This necessitated the extra feature selection step, wherein we used traditional statistical techniques (likelihood ratio testing and R-squared evaluation) to select the most suitable covariates to be included from a wide array of clinical data. While the clustering process remains the core of the predictive analysis, using statistical techniques for covariate selection is a robust and established practice when defining the initial model to be trialled for a machine learning algorithm. This is especially true in computationally heavy tasks such as longitudinal clustering of large datasets.[337]

5.2 Method

To create a predictive system as a basis for a renal monitoring guideline, we used the processed data from chapter 4 and put it through a model-based clustering algorithm. The aim was to create clusters that explained the pattern of renal change over time in similar patients. New patients can then be assigned to each cluster and from there their renal change can be predicted based on the overall cluster outcome.

5.2.1 Data used

As discussed in chapter 4, we used a processed dataset of 3800 adult patients with chronic heart failure, spanning from 1/1/2008 to 1/8/2016. The inclusion and exclusion criteria can be found in section 4.2.6. The whole dataset was split into training and test subsets.

The training set consisted of 2704 patients, two-thirds of the whole dataset, and this was used to run the clustering algorithm, and generate the output clusters. This is known as training since the algorithm 'learns' the characteristics of each cluster from this input data.[281] Once the training is complete the properties of each cluster are fixed.

The test set consisted of 1096 patients, one-third of the dataset, and this was used to validate the cluster outputs. The data is treated as if it was prospective patient information, and the algorithm is tested to see whether it assigns the correct cluster to each patient. This is used as a measure of stability for the algorithm and is used to assess the extent of overfitting.

5.2.2 Following on from feature selection

In order to create the initial clustering algorithm, we trained it using an assumed model of relationships between log(creatinine) and selected covariates that were likely to explain it. However, clustering is a computationally heavy process because each additional independent variable needs to be matched to each other variable in the model, and compared iteratively in order to obtain the optimum cluster format. For this reason, each additional covariate increases the computation time exponentially.

Since we started out with a large number of covariates, we needed to narrow down this list to as few as possible while still explaining renal function. To this end, we used the outputs of our feature selection step (as described in section 4.5) to select the optimal covariates to input into the model.

5.2.2.1 Selection method

From our feature selection results we can find the correlative status of each covariate studied in our dataset, however many of these variables inherently interact.

Table 5.l shows a streamlined summary of the feature selection results, for the purpose of choosing the optimal variables to progress into the clustering algorithm. It lists all the significant covariates with correlation to log(creatinine) in ranking order of p-value within the training dataset. This table was compiled with respect to co-linearities, so that if a variable appeared that was significant, all other similar variables with a greater p-value were excluded because having two variables with the same information would reduce the accuracy of the predictive model, e.g. systolic blood pressure removes the 'hypertension' and 'pulse pressure' variables. Similarly, the whole drug category columns were a better fit than individual drug columns so the individual drug categories were removed.

Table 5.1 Summary of linear mixed model regression (feature selection step) results showing correlates with log(creatinine) using training dataset, with co-linearities excluded

Rank	Variable	BHcorrP.val_2thirds	P.value_2thirds
1	Serum Urea	1E-246	< 1e-246
2	Serum Potassium	1E-246	< 1e-246
3	Loop Diuretics category	9.9e-169	5.4e-170
4	Antimicrobial category	3e-117	1.8e-118
5	Aldosterone antagonists category	2.8e-111	1.9e-112
6	Serum Albumin	6.2e-108	4.5e-109
7	Thiazide diuretics category	2.2e-89	2e-90
8	NSAIDs category	1.9e-77	1.8e-78
9	Serum Sodium	8.8e-63	1e-63
10	Systolic blood pressure	1.8e-62	2.1e-63
11	Days since diagnosis: diabetes	3.5e-55	4.4e-56
12	BMI	2.4e-34	3.5e-35
13	ACEi category	2.2e-32	3.4e-33
14	MCV	1e-21	1.9e-22
15	ARBs category	4.2e-14	9e-15
16	Atrial fibrillation	4e-09	1e-09
17	Anaemia	9e-09	2.3e-09
18	Smoker	1.2e-07	3.7e-08
19	Ischaemic heart disease	3.2e-05	1.2e-05
20	Peripheral vascular disease	0.0021	0.00092
21	Immunosuppressants category	0.012	0.0059
22	Practice ID	0.022	0.011

Using these outputs from the training dataset, we can surmise that the listed 23 features can be used as covariates in a machine-learning algorithm for renal function prediction over time. However, in order to minimise the number of included variables, it is useful to consider the strongest correlated covariates first. Since serum urea and serum potassium appeared to have similar strength of correlation with creatinine, we investigated their performance in more detail, along with that of the other strongly correlated features, to check for suitability of selection.

The p-values from the feature selection so far have referred to the likelihood ratio value obtained by pairwise comparison of the null model and a model that is null + one other variable. In order to further define the variance explained by each feature, we started with our null model (time since heart failure + age at heart failure diagnosis + gender ~ log(creatinine)) and we began to add in features in order of p-value in a step-wise manner. We then compared the percentage R-squared value between models of different numbers of variables. R-squared is a goodness-of-fit value that gives information about how much of the variance of the output is explained by the model, with a higher percentage giving a greater explanatory potential of the model. In this case, the R-squared for each linear mixed model equated to how well the model explains changes in log(creatinine) over time (in other words, how closely any given model fits with the regression line from the real data).

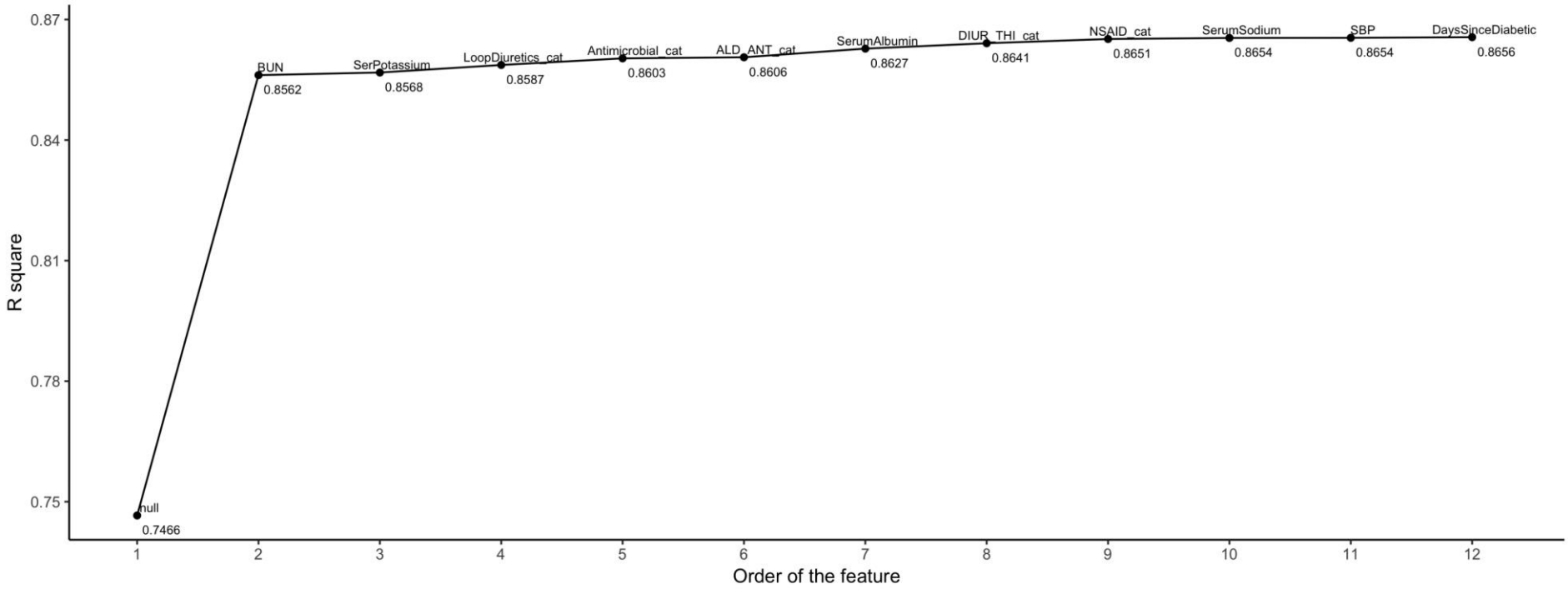

Figure 5.4 Stepwise forward regression of the null model
Adding consecutive variables to the null model in order of p-value to assess the change in R-square value

Figure 5.4 describes what happens to the model's R-square value when adding sequential variables to the model, in order of lowest p-value from feature selection. The first step shows the value of the null model which has an R-squared of approximately 75%. Once serum urea (BUN) is added, this jumps to around 86%, an increase of 11%. Subsequent additions to the model only increase this value by marginal increments, and it takes a further 7 additional variables to increase the value by a further 1%. This alone could mean that serum urea is the best predictor for creatinine change, or it could be that the variables added on after urea are equally as effective, but that their explanatory potential in the model was simply overshadowed by the addition of urea and they may still have strong predictive potential on their own in a lone model.

For this reason, we also made comparisons of the R-squared using the null model plus one additional variable, and we swapped this additional variable for each of the highest-ranking ones from our feature selection. This was to see how well these variables would perform in isolation, without the impact of urea in the model. Figure 5.5 shows the results of this analysis.

As shown, adding any other feature to the null model besides urea causes a minimal increase in R-squared value; however, urea retained its explanatory potential of around 11% regardless. We can therefore surmise that, not only is urea the best predictor for log(creatinine) and hence renal function, but that the other strongly correlated variables cannot contribute meaningfully in explaining the variance.

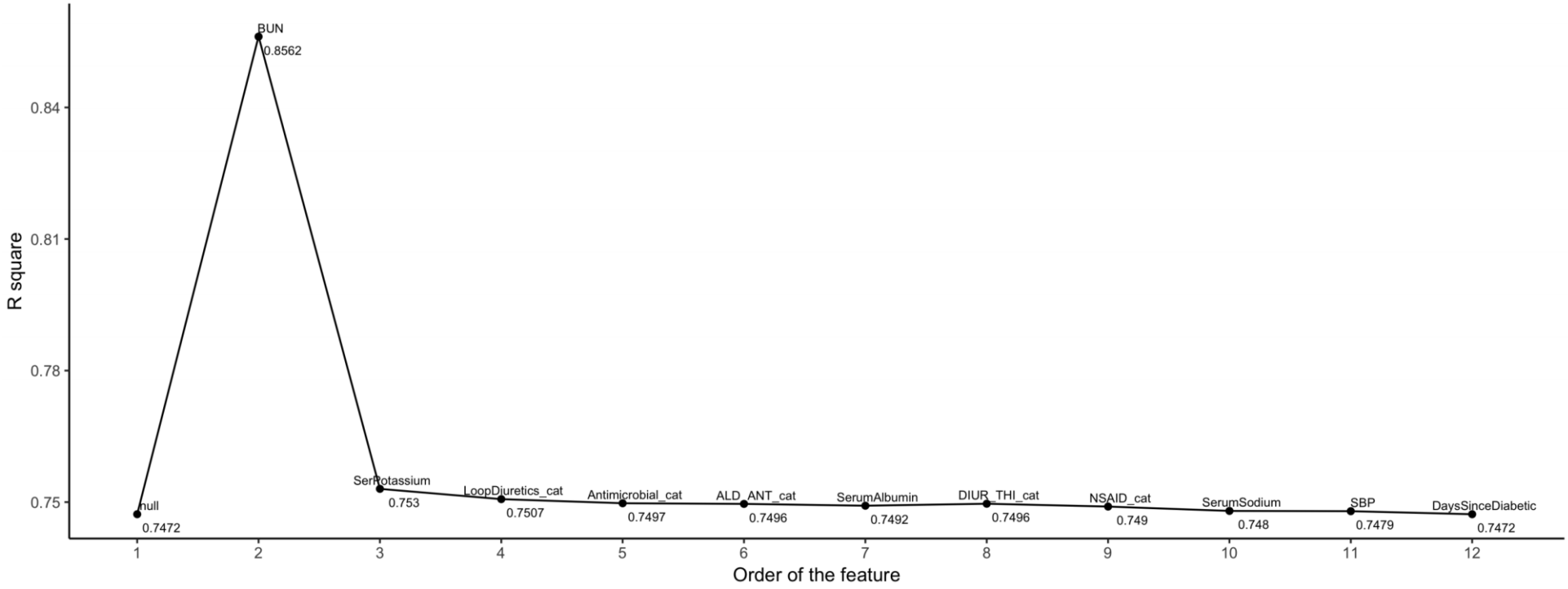

Figure 5.5 Score comparison of the R-squares of [null model + one additional variable] for the top-ranking covariates identified by feature selection

5.2.2.2 Features selected

The extremely strong correlation between urea and creatinine shown here is supported by previous studies that show urea levels are an independent risk factor for renal decline over time.[83] Since urea is filtered by the renal glomerulus, and its levels increase with a drop in urine output, it is expected that the serum levels coincide with creatinine which is also filtered out in the same way. Raised serum urea can also be found in both heart failure in and of itself as well as dehydration, which are both determinants of renal decline as mentioned in Chapter 1. This implies that out of all of the variables analysed, urea alone provided the benefit necessary to improve the predictive performance of our model, and would henceforth be included in any future versions of this model.

Therefore, b

ased on these analysis findings, the singular feature selected to be added to the model based on correlation with creatinine was serum urea.

In regards to the remaining model variables:

- Time as a factor, is measured via the two variables: age at heart failure diagnosis (hfage), and time since heart failure diagnosis. This allows us to differentiate the impact of exposure time with heart failure, taking into consideration the cumulative effect on renal function via cardio-respiratory syndrome (see Chapter 1).
- As we have seen in the previous chapter, we have found some distinct differences between gender groups. We have added in the gender variable to distinguish between these groups and provide more personalised predictive approach.

- In order to distinguish the effect of deprivation on outcomes of renal function, we also added IMD decile to the model itself. IMD has shown precedent in similar validated statistical risk models looking at renal decline (see Table 4.1). Although IMD was not a significant correlate in the model, this was likely related to the biased distribution of patients mostly in the deprived deciles in the SIR dataset. Furthermore, since this is based on GP-level IMD, and the test data is used in different GP practices, differentiating IMD would help reduce overfitting from the current training set, by allowing the algorithm to compensate for different locations. Therefore, in order to make the model generalisable at a population level, IMD was included

The final model taken forward for clustering was therefore:

Log (creatinine) ~ time since heart failure + age at heart failure diagnosis + gender + serum urea + IMD decile

5.2.3 Model-based clustering: flexmix

We used the R package flexmix in order to cluster the data.[338] Flexmix is a model-based longitudinal clustering algorithm which is computationally efficient and shows logical clustering patterns even in small samples. It can deal with multiple independent variables and can also flexibly incorporate multiple different time points per patient. In addition to this, it can self-select the optimal number of clusters, which reduces the experimental steps before finalisation. Flexmix therefore met all our needs for training with our processed dataset and provided a workable clustering environment to use as a foundation for predictive analysis. Since we had no prior knowledge of the optimum

number of clusters, we allowed the algorithm to converge, first testing for the starting number of clusters, and then the final cluster number. This was done via multiple cycle iterations to find the cluster solutions that had the highest performance.

5.2.4 Validation

Once the algorithm had converged with the optimal number of starting and final clusters, we took the best performing cluster solution and applied it to the test dataset. This was done to validate the cluster output internally and assess the accuracy of cluster assignments.

5.3 Results

5.3.1 Setting the number of clusters

The starting number of clusters (*K*) was tested in a range from 1 – 20 to explore the cluster space. For each given *K* we ran the model 50 times to examine cluster stability in each iteration. The computational time took 4 days. The model stability was examined using the Integrated Completed Likelihood (ICL) criterion. This is a modified version of Bayesian Information Criterion (BIC) that measures posterior probability, while accounting for a measure of uncertainty in the form of entropy.[339] The posterior probability is the probability that each data point has been assigned to the correct cluster by the end of the clustering process. A higher posterior probability therefore means that the clusters are well defined and that the algorithm is able to effectively differentiate between them with minimal overlap; i.e. each cluster is sufficiently different from each other such that assignment of new data has more certainty of belonging to a specific cluster. In contrast, a lower ICL means that the

posterior probability for the model has obtained less penalty for the number of parameters and the amount of entropy. Therefore, the lower the ICL, the lower the measure of uncertainty, and hence the more robust and accurate the model is.

We looked for the model with the lowest ICL out of the runs conducted, with respect to determining the starting *K*. Convergence of the final number of clusters (FCN) was handled by the EM algorithm integrated within flexmix as previously described. Based on this initial clustering analysis of 50 runs each (Figure 5.6), it was seen that the lowest ICL models converged when *K* was 5, 6, 7, 8 or 9. Each of these runs converged into an FCN of 1-10.

To examine this further, we ran *K* as these five numbers for an additional 120 cycles each, in order to determine the best starting *K*. After these cycles, the lowest ICL model emerged using *K*=9 and final cluster number = 7. Figure 5.7 shows a box-plot with the ranges of ICL found with different *K* starting clusters 5 – 9. It can be seen that while the mean of the ICL in *K*=8 is the lowest, the smallest observed value belonged to *K* = 9.

After these 120 cycles, the most stable model with the lowest ICL converged at final cluster number of 7 (Figure 5.8). As a result, further cycles from that point onwards used *K* = 9 and FCN = 7 to explore the cluster space further.

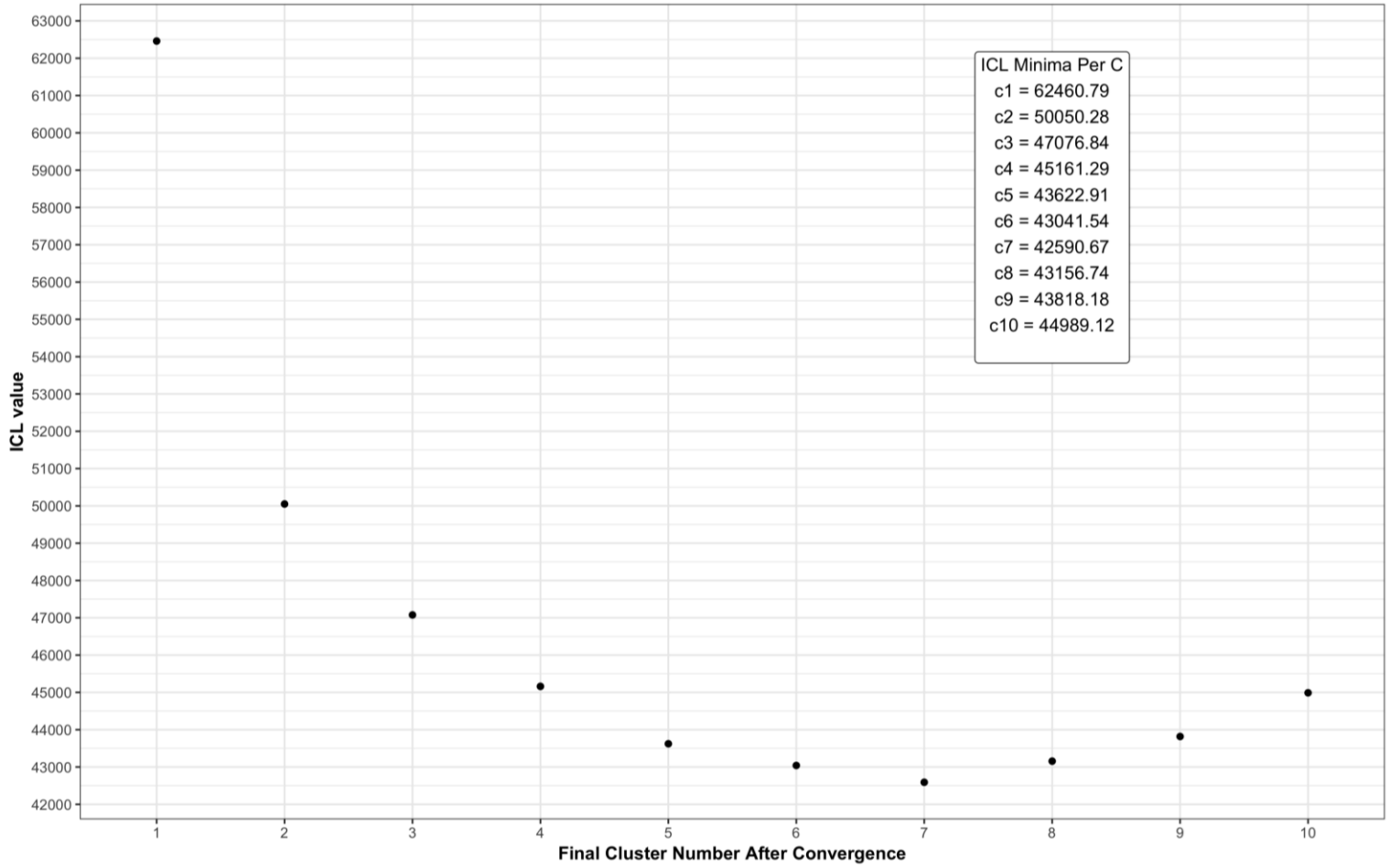

Figure 5.6 Result of initial analysis running *K*=1-20, run 50 times for each *K*, resulting in FCN 1-10

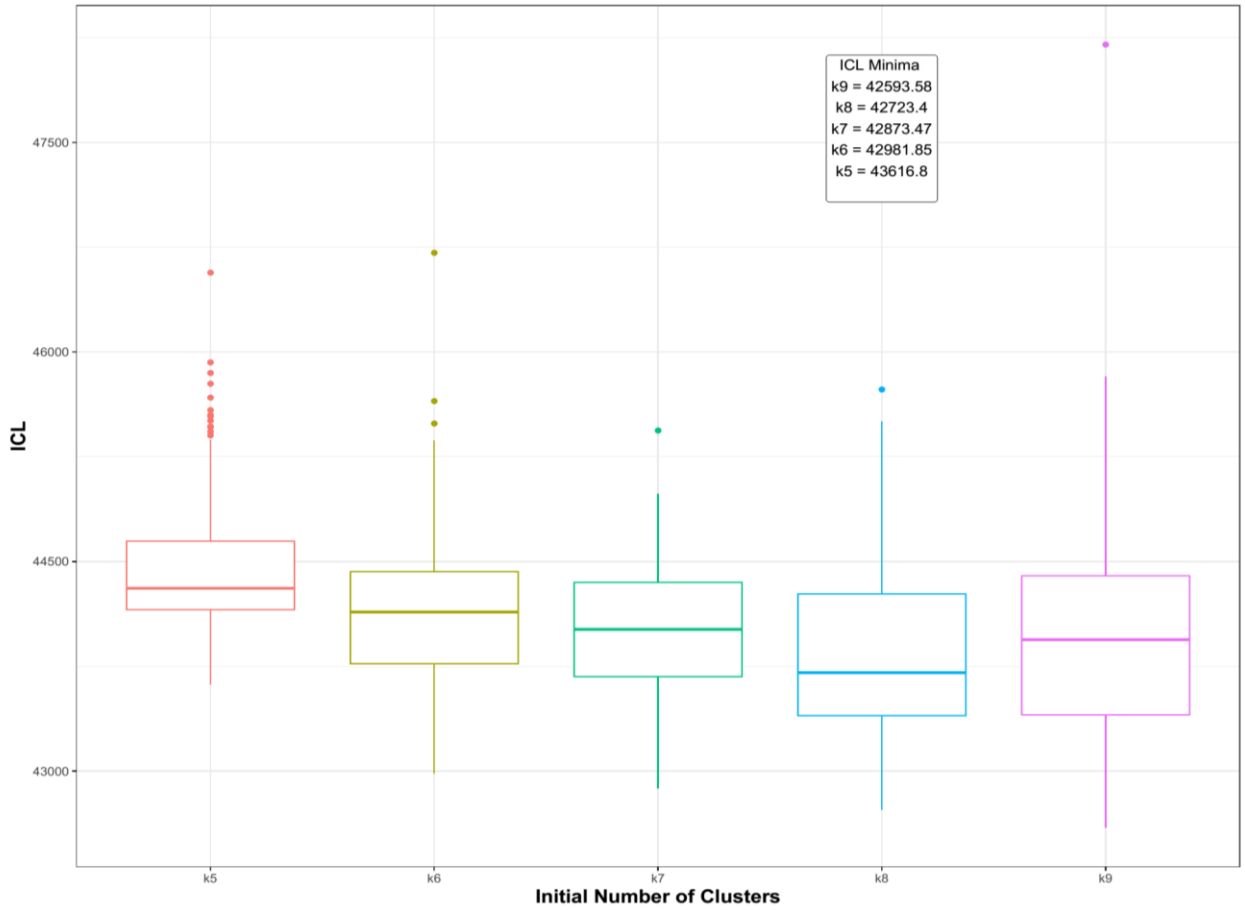

Figure 5.7 Boxplot of ICL values with different number of *K* starting clusters 5 – 9, after 120 runs of each *K*

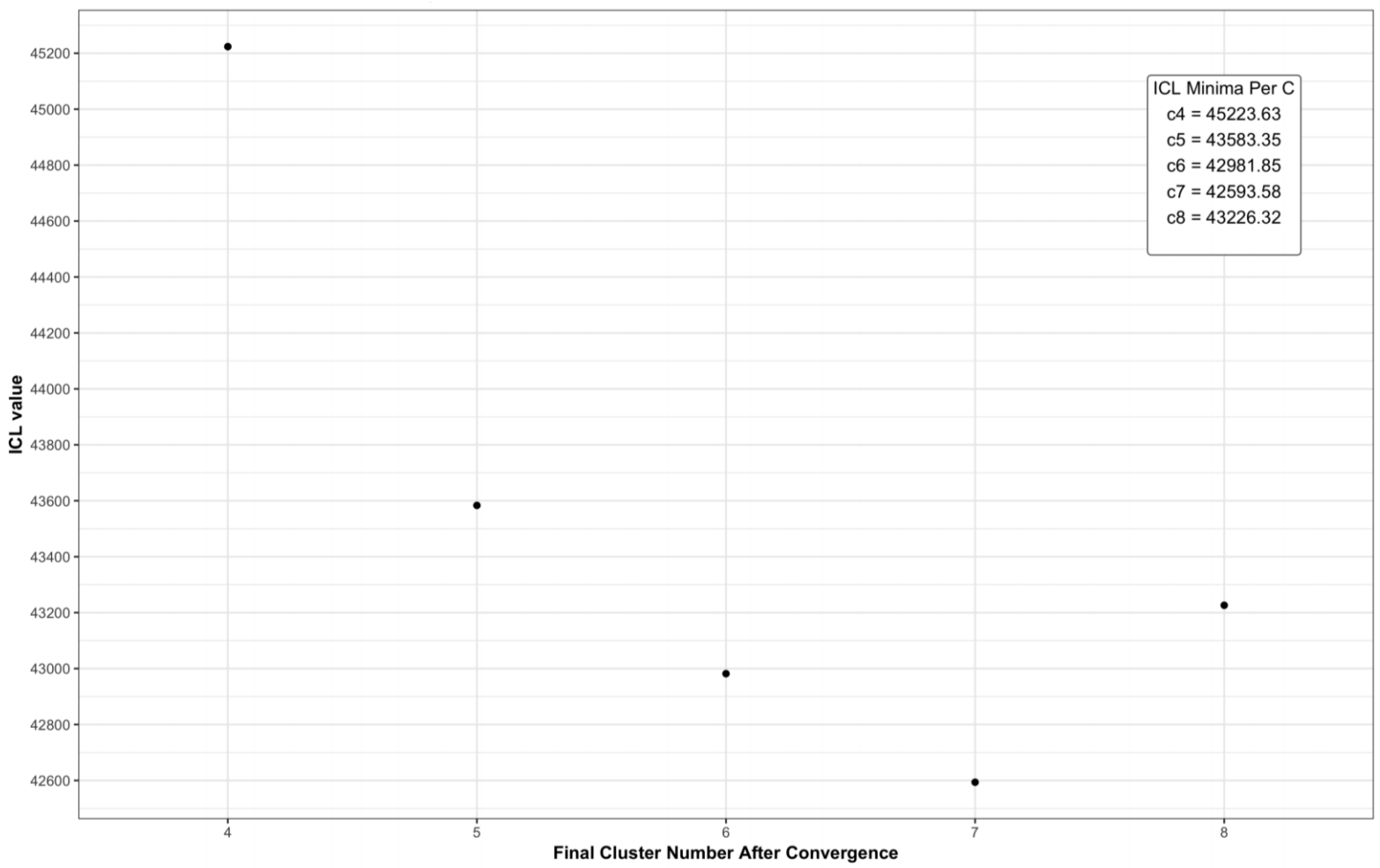

Figure 5.8 ICL values relating to final cluster numbers, after 120 runs each of *K* from 5 – 9

5.3.2 Clusters generated

We thus ran another 300 trials of clustering with K = 9 and FCN = 7, using random starting points in order to find the most stable model to use for prediction. Figure 5.9 below shows the distribution of ICLs found for each cycle.

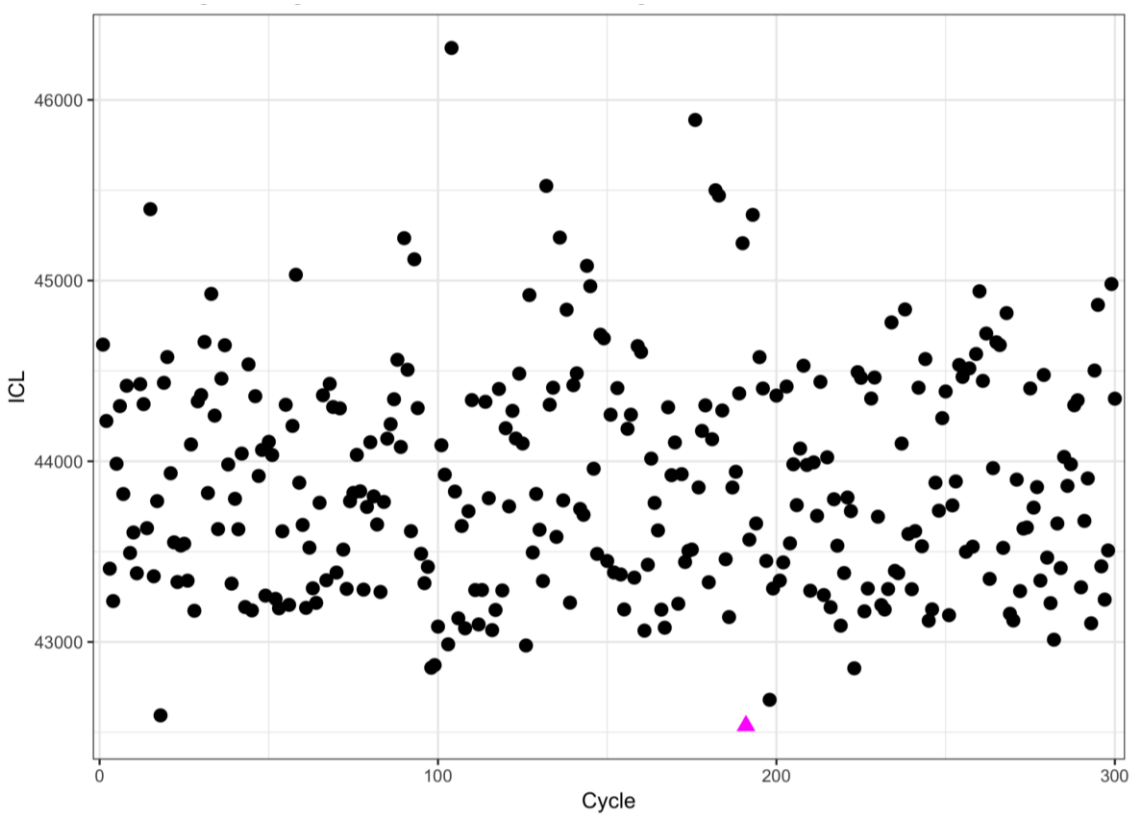

Figure 5.9 ICL results of 300 trials of clustering with K = 9 and FCN = 7
The data point marked with a triangle highlights the model with the lowest ICL

The ICL over these 300 trials was in a range between 42536.50 – 46284.52 (mean=43889.27, sd=613.98). The lowest ICL model had a value of 42536.50 and this was the final model which was carried forward for validation.

5.3.2.1 Cluster stability

Once the cluster solution with the lowest ICL was selected, the posterior probabilities of each patient were calculated with respect to the clusters assigned to them. This is a measure of how certain a patient is to belong within each cluster. Each patient was assigned to the cluster for which it had the highest probability of belonging to, according to the clustering algorithm. Figure 5.10 below shows histograms for each cluster demonstrating the posterior probability value of patients within that cluster.

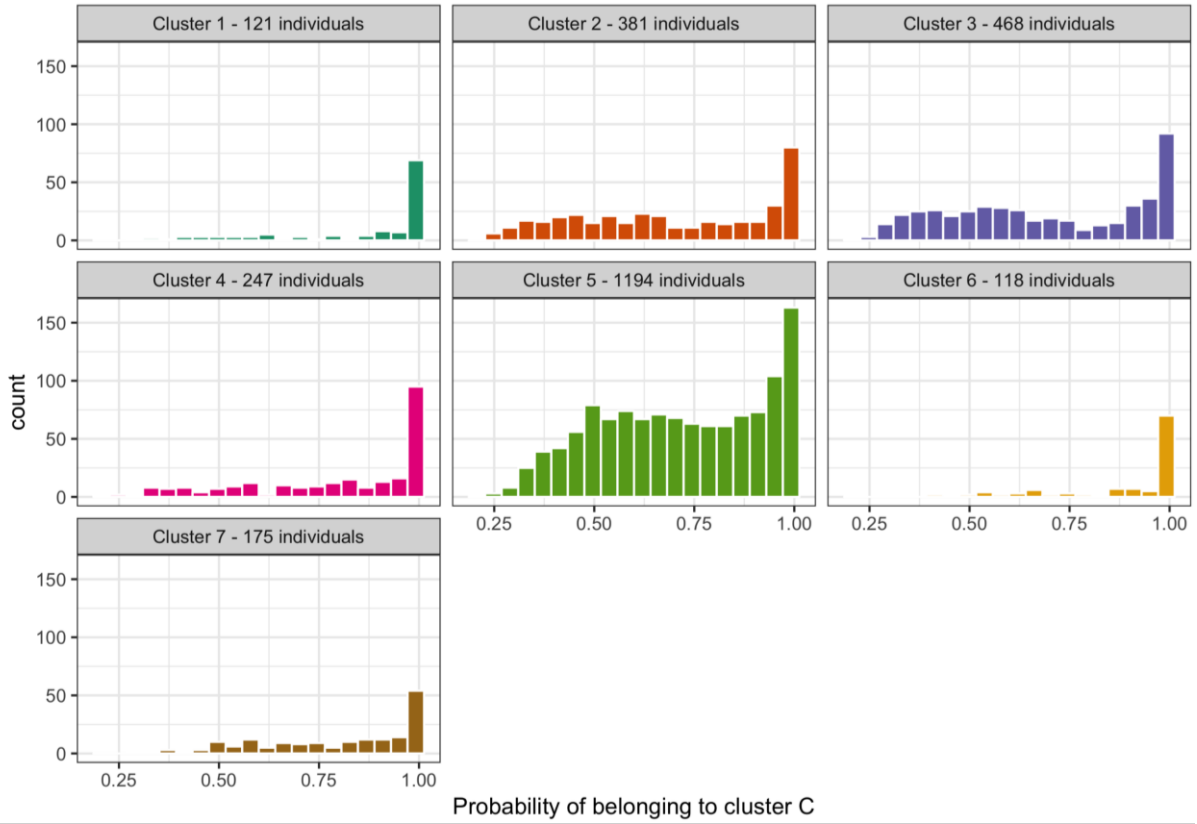

Figure 5.10 Histogram charts showing the number of patients and the probabilities of belonging to their assigned cluster, for each cluster from the training set (n=2704)

As we can see from the histogram charts, in each cluster, the highest proportion of patients were those with near 100% probability of belonging to that cluster. This means that the clusters generated were well defined and that patients mostly fit well into one

of the seven clusters generated. This indicates that our clustering process was successful in generating distinct explanatory groups with respect to renal function over time.

5.3.2.2 Cluster characteristics

Distribution

Figure 5.11 shows the residual plots of log(creatinine) over time, along with the regression line for all seven clusters in this selected model.

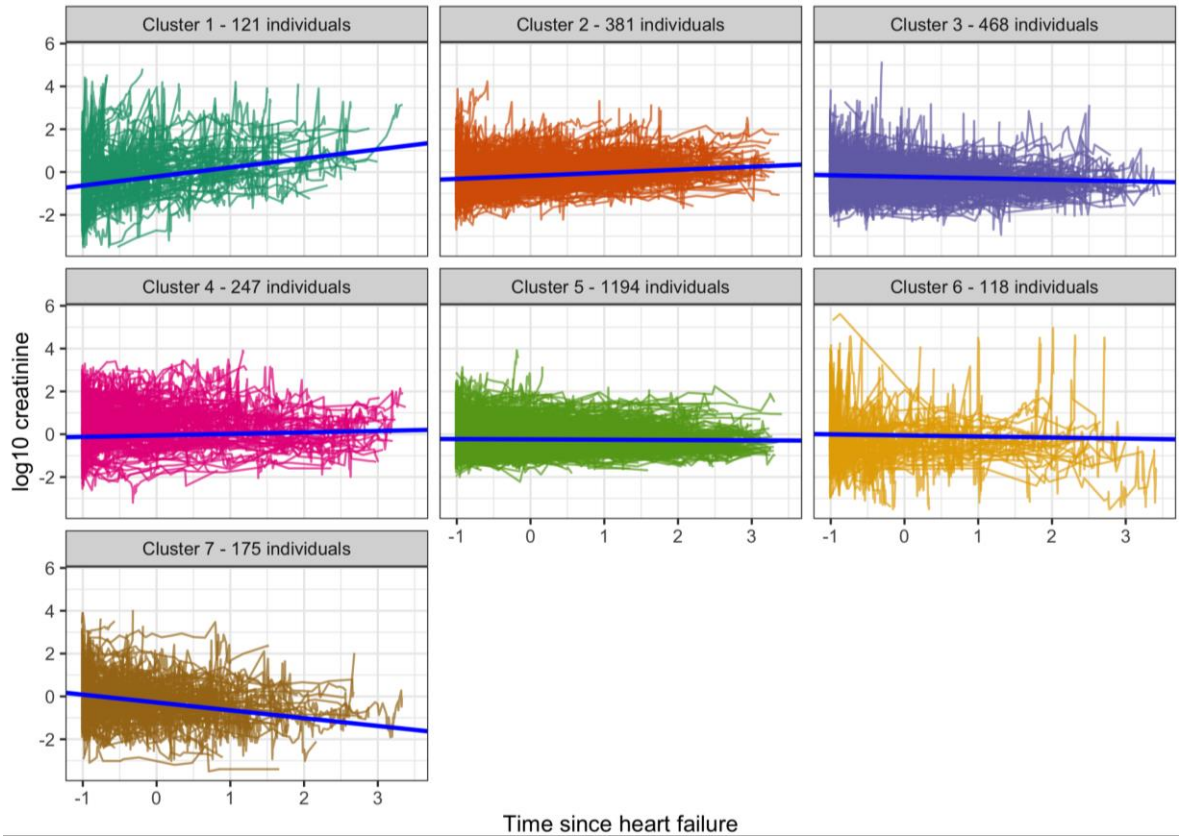

Figure 5.11 Residual plots showing trajectories of log(creatinine) over time for patients in each cluster within the training dataset (n=2704)

As shown, seven distinct model-based clusters were created, each with their own characteristics. Not only was the trajectory different in each case, but the spread of the data appeared concordant with other data points within that cluster. To further demonstrate the spread of each cluster, Figure 5.12 below shows the relative distribution of different log(creatinine) values per cluster.

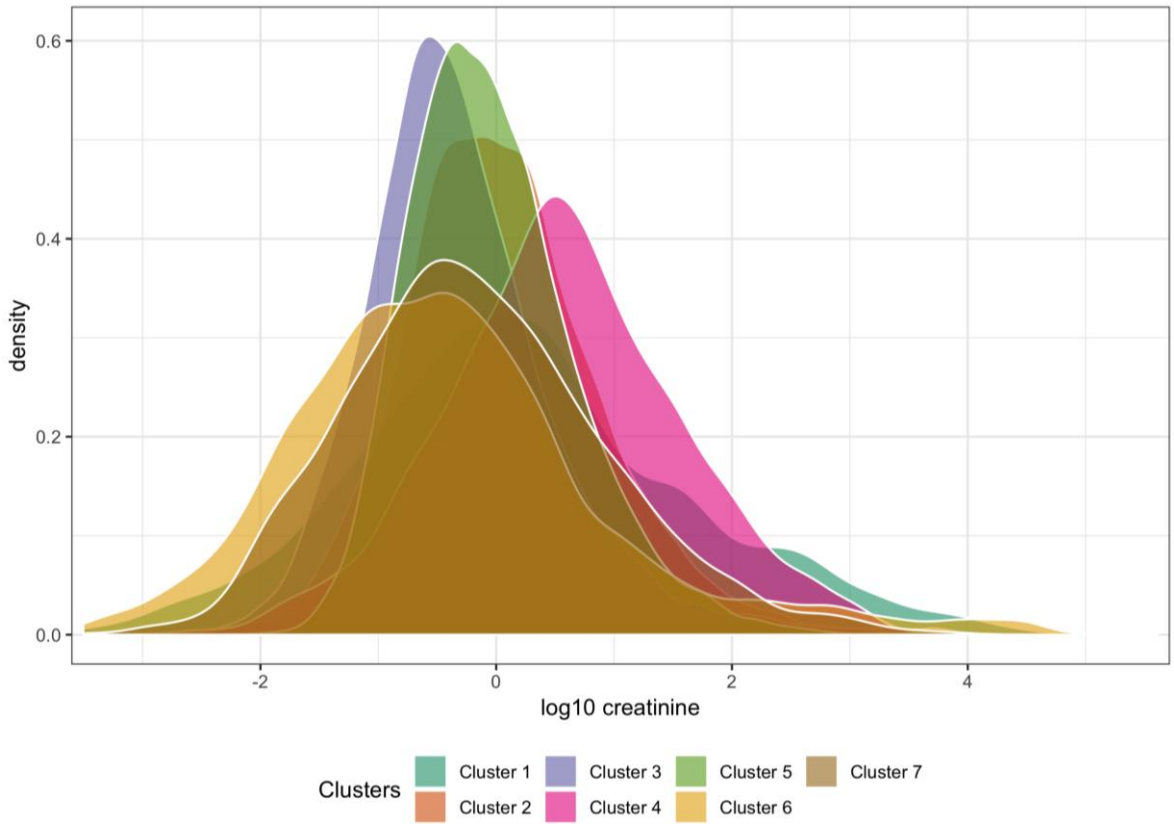

Figure 5.12 Log(creatinine) distribution per cluster in the training dataset

The figure above demonstrates that not only were each of the densities of renal function data different for each cluster, but that log(creatinine) was normally distributed. The different position of the peaks of each cluster can suggest where the greatest density of creatinine lies. The greater the right-shift of the log(creatinine) peak, the worse the renal function of the patients within that cluster.

Trajectory

We can quantify the cluster trajectories by calculating an estimate of the slope in each cluster. This is useful in determining which clusters are higher risk than others, by suggesting which patterns of renal function decline quicker than the rest. A negative estimate means that log(creatinine) has a downward trend over time within that cluster, which in turn lowers the risk of renal dysfunction. On the other hand, a positive slope estimate equates to increasing log(creatinine) and hence renal decline, and the greater the positive value, the faster the relative deterioration (with a steeper slope). The slope estimates along with 95% confidence interval can be found in Table 5.2 and Figure 5.13.

Table 5.2 Tabulated slope estimates per cluster with 95% confidence interval (SE = standard error)

Cluster	Slope estimate	Slope SE	Lower bound	Upper bound
1	0.5157	0.0169	0.4827	0.5488
2	0.1452	0.0057	0.134	0.1565
3	-0.1138	0.0058	-0.1251	-0.1024
4	0.0764	0.0064	0.0656	0.0908
5	-0.0078	0.0031	-0.0139	-0.0016
6	-0.0764	0.0187	-0.1131	-0.0396
7	-0.4415	0.0127	-0.4664	-0.4166

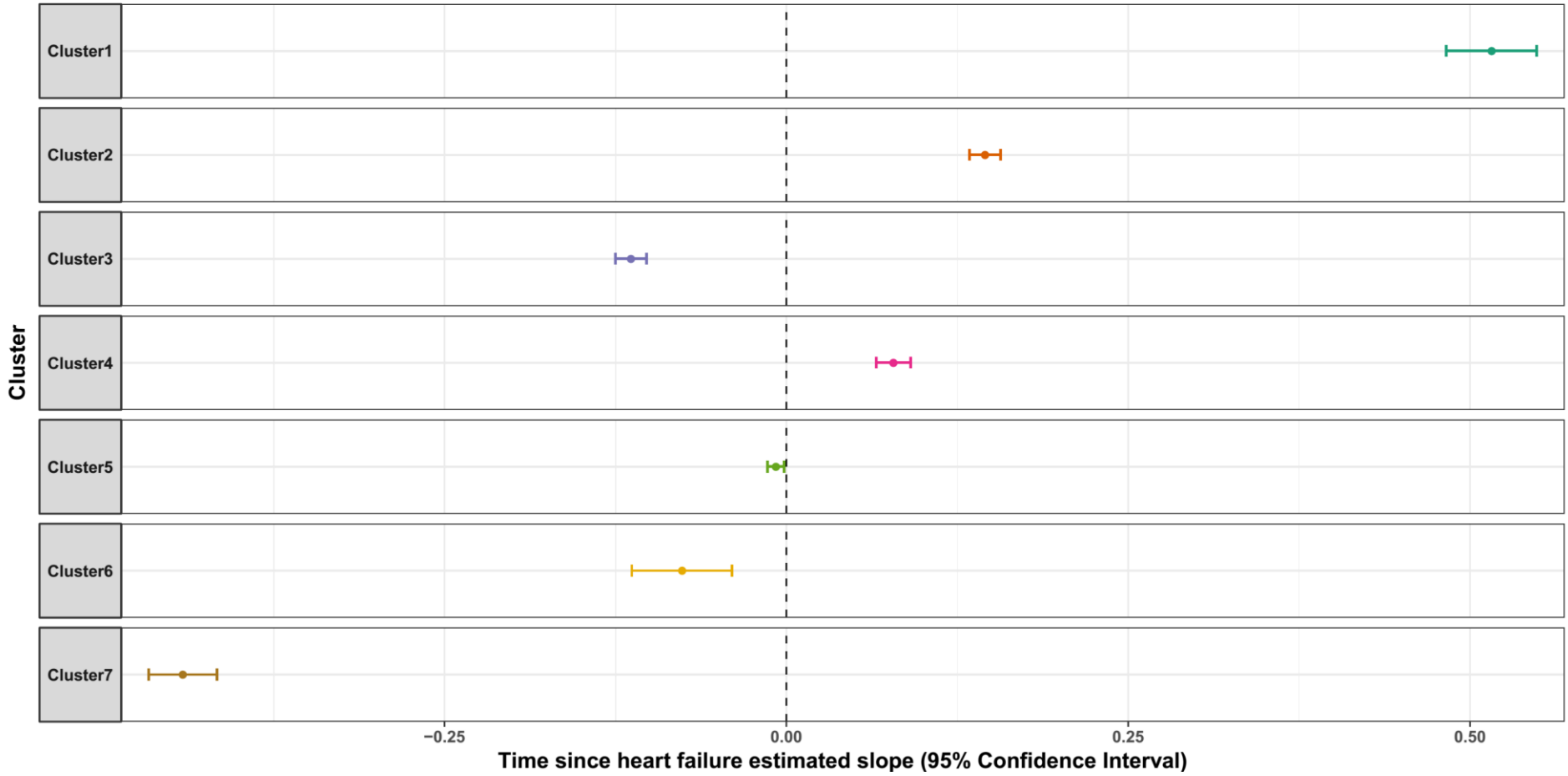

Figure 5.13 Variations of the slope estimates per cluster

From these figures we can see that clusters 3, 5, 6, and 7 had a negative slope estimate, i.e. the creatinine trends downwards over time, reducing risk of renal decline. However, clusters 1, 2, and 4 had a positive value, which suggests the patients within that cluster had an increasing creatinine trend over time, and thus a higher risk of renal decline. It is worth noting that cluster 5 had the estimate which was closest to zero, and thus may have been closer to having a neutral creatinine over time. These findings allow us to make inferences as to risk category of new patients based on cluster assignments alone. As noted earlier, the steepness of the slope indicates rate of change and so ranking the clusters in order from most rapid to least rapid renal decline gives us the following order of renal risk severity: 1, 2, 4, 5, 6, 3, 7. This can be observed visually from Figure 5.13. It is important to note that the slope defines change over time in terms of the log(creatinine) so the raw creatinine change is an exponential of this value, and the slopes should be likewise interpreted as an exponential directional change.

5.3.3 Results of validation

Validation involved taking the outputs of the cluster generation and applying them to the test dataset, which included 1096 patients that were not included in the training data. The following cluster plots (shown in Figure 5.14) emerged when assigning the test data to the formed clusters.

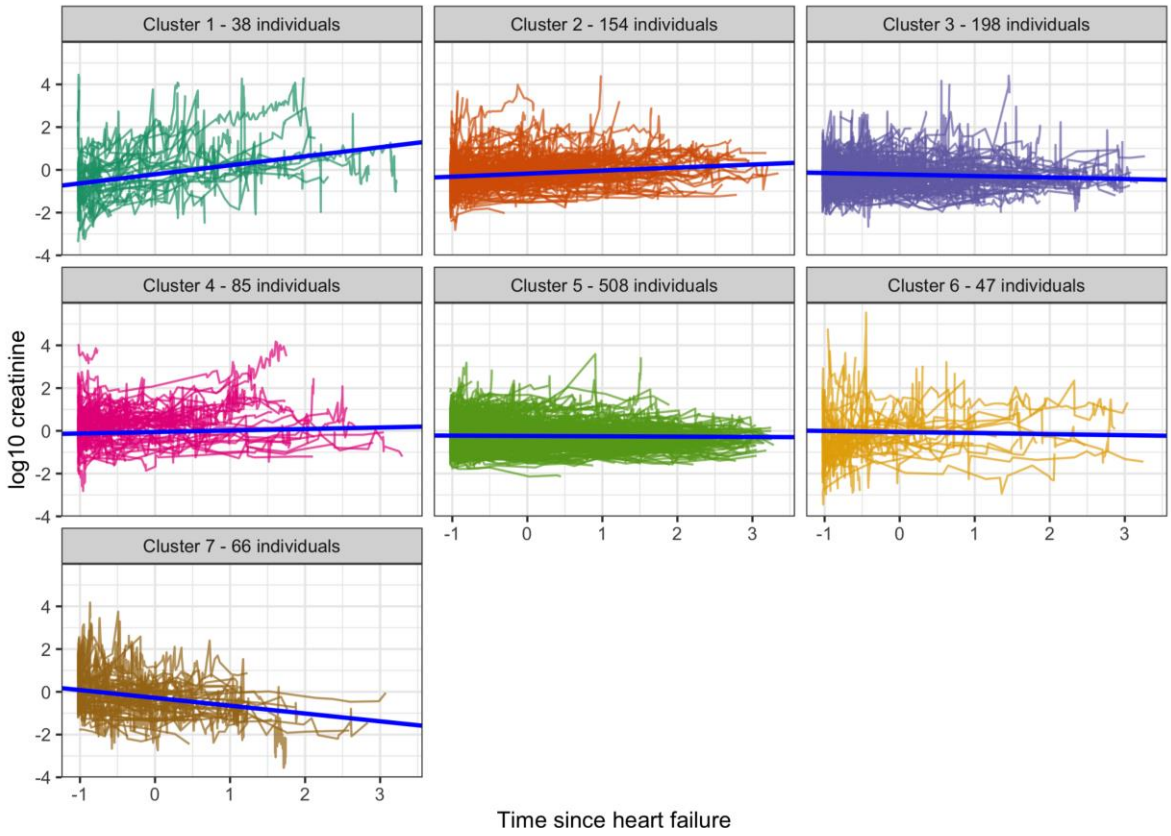

Figure 5.14 Residual plots showing trajectories of log(creatinine) over time for patients in each cluster within the test dataset (n=1096)

Visually the groups appeared distinct within their own clusters. Clusters 1, 4, 6 and 7 had less than 100 patients assigned each, and cluster 5 remained the most predominant cluster at over 500 patients. Looking at a plot of the densities of each cluster in the test set, we observed that the visual representation in Figure 5.15 matches that of the training set.

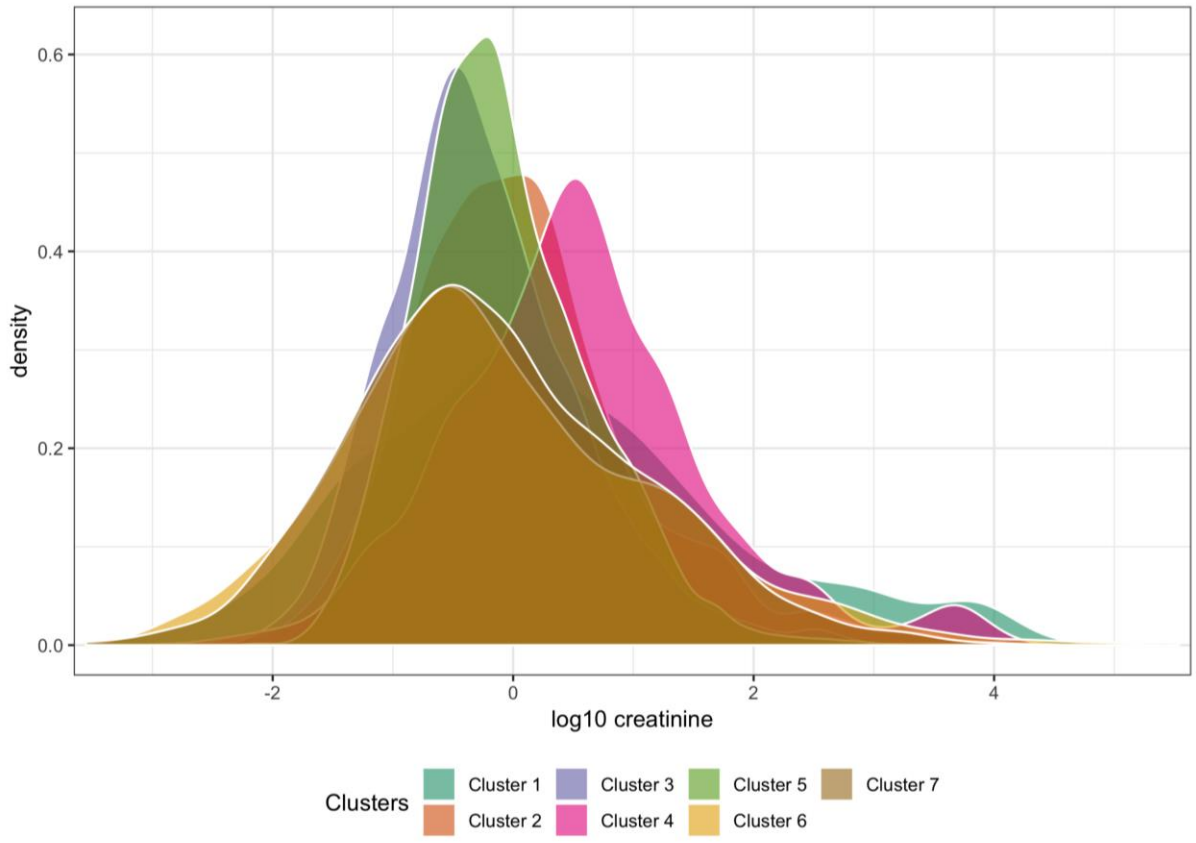

Figure 5.15 Density of log(creatinine) values in different clusters using the test dataset

Compared to the training set, the peak of cluster 4 was again around the log(creatinine) value of 1. The peaks of clusters 5 and 2 were centred around 0, with the peak of cluster 3 closely behind this in the negative scale. Clusters 6 and 7 were also left-shifted, although cluster 7 was perhaps more shifted towards the negative scale in this test dataset than in the training set. The similarity in densities showed that new data entering the algorithm was classified in a predictable manner, and that the clusters created were robust. The measure of clustering predictive performance can also be viewed by observing the posterior probabilities in the test dataset, a measure of its cluster assignment performance on new data (Figure 5.16).

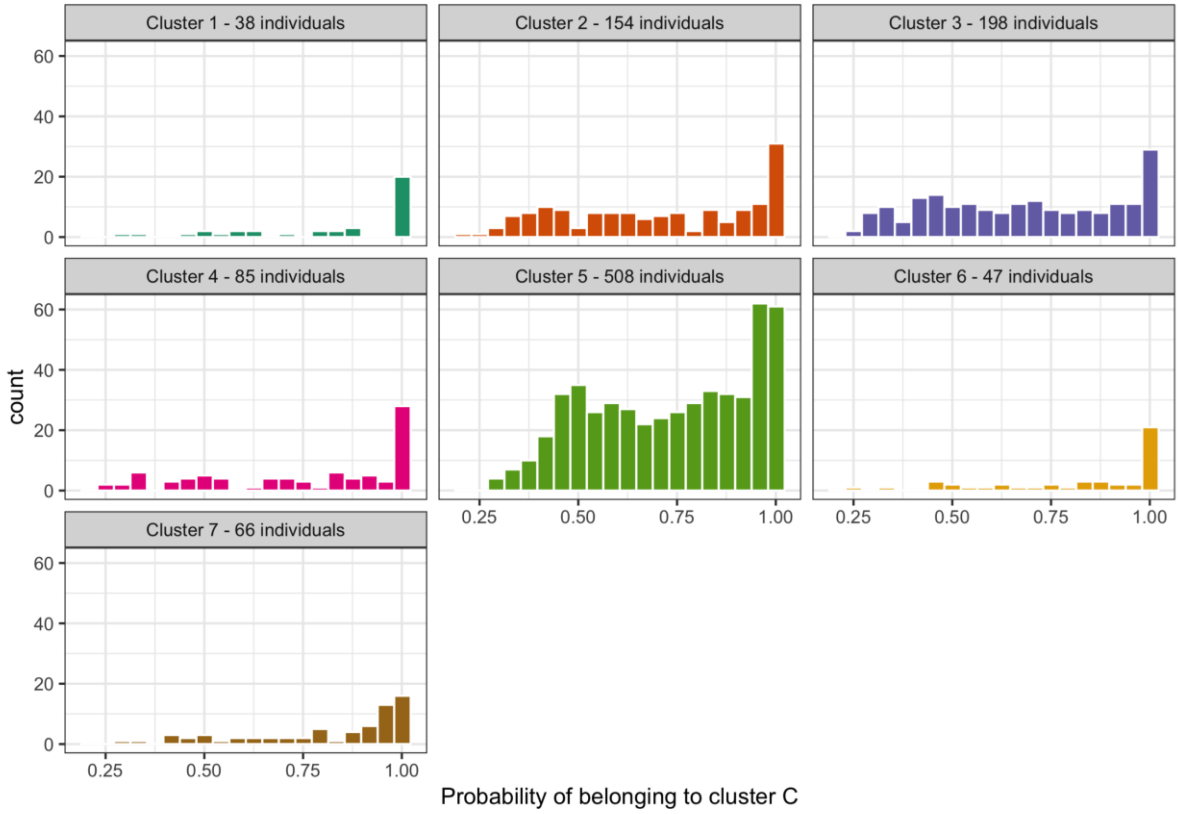

Figure 5.16 Posterior probabilities of cluster assignment of patients within the test data (n=1096)

There were extensive similarities in the probabilities between test and training data. In all clusters, there was a high frequency of patients close to the 100% posterior probability category. This was most marked in clusters 1, 4, and 6, and to a great extent in 2 and 3 also, which shows that these clusters had high discriminant rate for patients belonging within them. In the test data, the probability in cluster 7 was less well pronounced towards 100% compared to training data, but still well shifted towards the right-hand side, indicating the majority of patients had a high posterior probability. In cluster 5, there were higher frequencies of patients across the probability range from 40 – 80%, and this was shown to be the case in both training and test data. Incidentally, cluster 5 was the most frequent cluster assignment, containing 508 patients out of 1096

in the test set, almost half the entire dataset, and in the training data it encompassed 1194 patients out of 2704.

5.3.4 Differences between cluster groups in test data

As the completed algorithm was applied to the test dataset, we looked at the characteristics of the cluster groups to determine whether there were observable differences in the included covariates for each cluster.

Table 5.3 shows a snapshot of the final cluster assignments at the end of the study window. However at any point during the patient's longitudinal data, they may change assigned clusters, which would shift the demographics and characteristics of each cluster dynamically at different points in the study. Analysing these clusters in this way is sufficient to show eventual differences which emerge between cluster groups, however this snapshot is not sufficient to explain how the assignments are configured over time as more longitudinal data is added.

Cluster 1, identified as having the steepest positive slope estimate in table 5.2, which could indicate the highest risk of renal decline, appeared to have the greatest average creatinine and urea values throughout all the clusters. In addition, this cluster had the highest rate of testing over time, and the greatest average number of tests per patient than the other groups. This supports the indication that cluster 1 was assigned to the patients most at risk of renal decline, with the greatest renal biomarkers and more frequent testing. In contrast, cluster 7, which has the most negative slope estimate, did not have the lowest creatinine, urea, or the lowest frequency of monitoring, however, it did have the highest average age at heart failure diagnosis (79.67). This may indicate that the cluster group was assigned to older patients who had a high baseline creatinine due to age, but whose renal function remained stable over time.

Table 5.3 Characteristics of patient groups from test data clustering

Cluster	C1	C2	C3	C4	C5	C6	C7
N	38	154	198	85	508	47	66
Males	16	76	99	45	334	25	31
Females	22	78	99	40	174	22	35
Mean creatinine (umol/L)	132.38 ±99.19	104.92 ±53.06	97.09 ±41.58	136.80 ±72.68	95.42 ±30.79	106.98 ±52.19	106.78 ±56.14
Mean BUN (mmol/L)	12.3 ±5.27	9.52 ±5.07	8.25 ±3.59	13.43 ±7.03	7.95 ±3.57	8.28 ±3.25	10.16 ±5.39
Mean age at HF diagnosis	75.5 ±8.97	75.3 ±10.62	73.4 ±12.48	74.13 ±13.08	70.61 ±12.91	71.43 ±11.68	79.67 ±12.14
Mean days between tests	31.51 ±33.36	66.88 ±66.24	66.61 ±73.97	54.16 ±134.23	125.8 ±133.77	44.35 ±39.4	52.94 ±64.75
Mean number of tests/pt	42 ±38	24.45 ±19.12	22.10 ±18.29	27.18 ±21.08	13.08 ±12.19	25.98 ±18.25	33.35 ±27.19
Mean follow up/pt (days)	1034.47 ±861.28	1231.81 ±881.47	1058.81 ±851.6	918.98 ±834.28	1202.2 ±914.06	952.11 ±882.58	1043.02 ±678.74

Most of the clusters had similar numbers of both male and female patients throughout. The exception is cluster 5 which appeared to have almost double the number of male patients as female. In addition, it was also the most commonly assigned cluster group. This indicates that there may be a predominant pattern of renal decline over time in heart failure patients and that this pattern appears more frequently in male rather than female patients. Cluster 5 also had the lowest average creatinine and urea with relatively low standard deviation, despite the high sample size, indicating that these patients are likely to remain at a stable level of renal function over time without much variability. Further, cluster 1 has the lowest average age at heart failure diagnosis from the other clusters (70.61). It is also interesting to note that this group has the lowest frequency of monitoring over time, as evidenced by the longest monitoring interval and the least number of tests per patient.

5.3.5 Evaluating variance

Here we considered the accuracy of the predictions gained from each of the training and dataset clusters by determining the level of variance found in the predictions. We measured variance by comparing R squared values for both the training and test set, and looking at related root mean square error (RMSE). The R squared related to how much of the variance of log(creatinine) from patients within a single cluster is explained by that cluster's regression model. In effect, this was a measure of how many observations fell within the regression line generated for each cluster. The RMSE is a standard deviation for the residual of log(creatinine) around the prediction, which can also mean that it is a measure of the error of prediction. It is a value that describes the distance of the observations away from the regression line, and so can be used to estimate how far our prediction is from the actual value. In this case, it is measured as

a value of log(creatinine) and the lower the RMSE, the closer the prediction is to the true value within that cluster, i.e. the lower the error of prediction. Table 5.3 shows the individual cluster values for R squared and RMSE for comparison of training and test data.

Table 5.4 RMSE and R squared values of training and test set clusters

Cluster	R squared Training set	R squared Test set	RMSE Training set	RMSE Test set
1	50%	47%	0.82	0.48
2	45%	80%	0.49	0.86
3	76%	64%	0.74	0.47
4	63%	62%	0.47	0.80
5	57%	55%	0.54	0.56
6	68%	38%	0.97	0.80
7	67%	67%	0.82	0.94

Table 5.4 shows that the R squared is similar in value in most of the clusters between the test and training dataset. The discrepancies were apparent more in clusters 2 and 6. In cluster 2 the training set explained 45% of the variance but there is better performance shown paradoxically in the test set, with 80% variance explained. A reverse pattern was shown in cluster 6 where variance explained is 68% in the training set but only 38% in the test set; however, the RMSE between groups in this cluster was roughly the same. The total calculated RMSE for the 7-cluster model was 0.64 in the training dataset and 0.65 for the test dataset. This confirmed that the model had not undergone extensive overfitting and matched well with new data, showing approximately equal predictive performance, on average, in both sets.

As for the accuracy of prediction, we visualised the impact of the RMSE value by plotting observed creatinine values overlaid with predicted creatinine values (Figure 5.17 for training data and Figure 5.18 for test data). This showed us how close our prediction was to the true data.

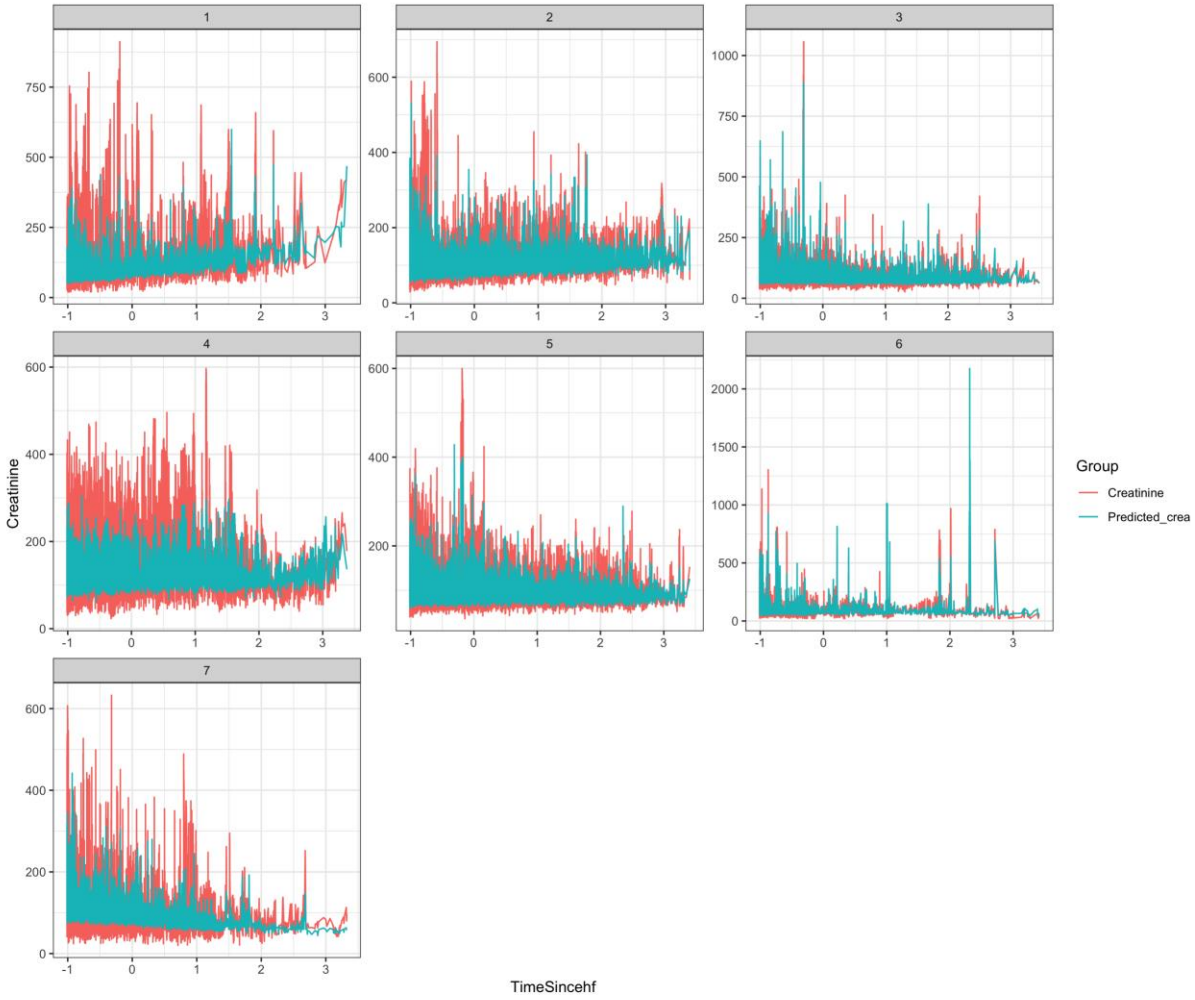

Figure 5.17 Plot of the training data, showing actual creatinine values and predicted values using final cluster output.

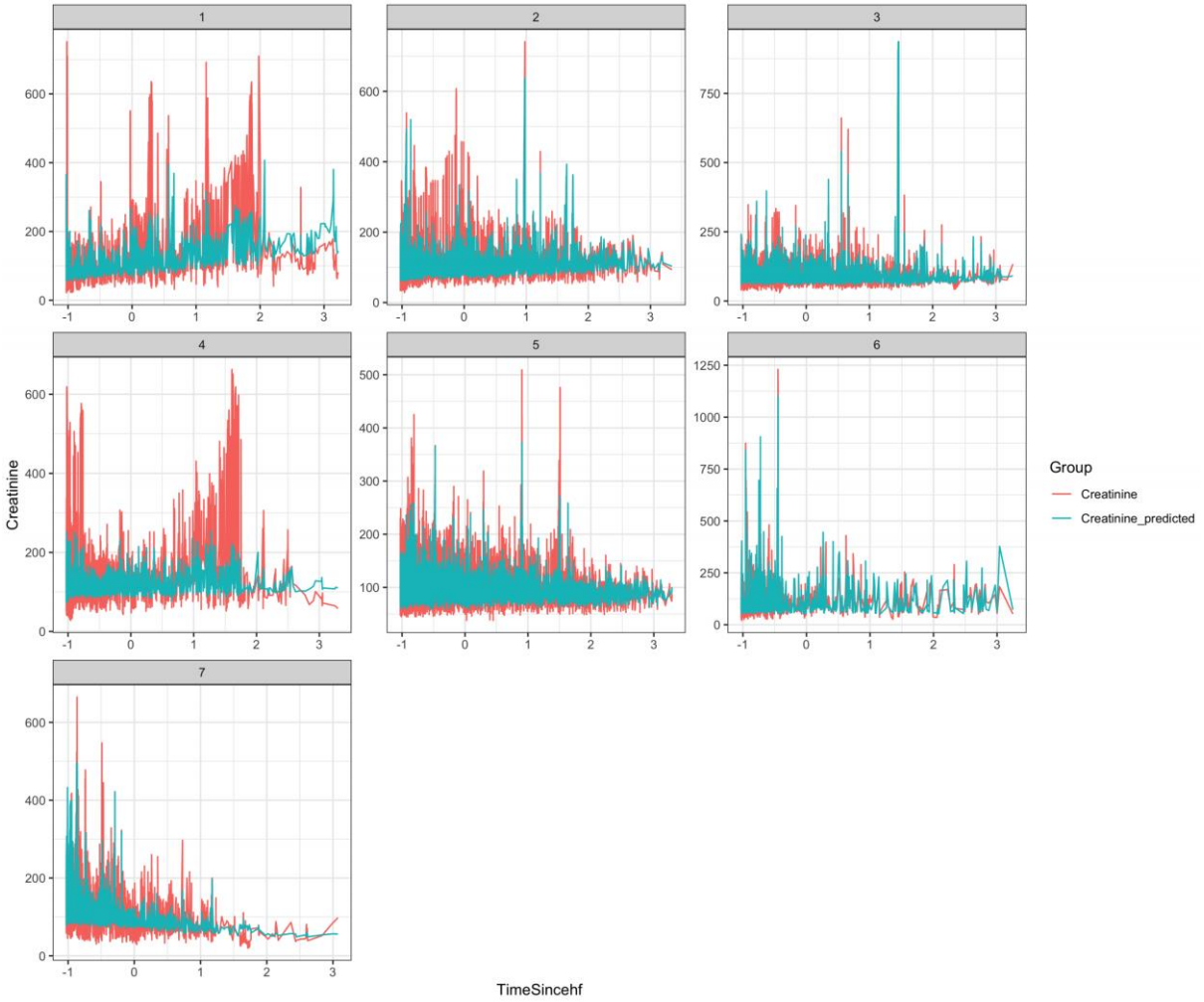

Figure 5.18 Plot of the test data showing actual and predicted creatinine values

We observed that while there were some visual similarities in the prediction outlines of all clusters, some marked disparities emerged when looking at the test data. This especially involved unpredictable peaks in clusters 1 and 4 of the test dataset. Fortunately, all other cluster predictions appeared roughly concordant with observed values.

To better evaluate RMSE for clinical interpretation, we exponentiated the log(creatinine) values so we could determine the deviance in raw creatinine. We found that the raw creatinine RMSE of the training data was 44.74 umol/L and for the test

data is 46.90 umol/L. While this confirmed that the predictive ability of the algorithm is consistent between the test set and the training set, it does not give much additional information in and of itself. It was more valuable therefore to calculate the percentage deviance of creatinine from the observed values than the raw creatinine. This can be done by measuring the mean absolute percentage error (MAPE). Furthermore, in order to explain any discrepancies noted from the visual plot of predictions, we need to look at the prediction error per cluster (Table 5.5).

Table 5.5 Predicted creatinine, RMSE, and MAPE values per cluster, comparing training and test datasets

Cluster	Dataset	N patients in the cluster	Range of Predicted Creatinine	RMSE	MAPE %
Cluster 1	**trainset**	**121**	**51.3 - 599.11**	**84.04**	**33**
Cluster 1	**testset**	**38**	**54.2 - 407.13**	**91.94**	**34**
Cluster 2	trainset	381	53.43 - 532.32	35.88	19
Cluster 2	testset	154	60.88 - 637.12	39.39	19
Cluster 3	**trainset**	**468**	**54.9 - 888.16**	**24.15**	**19**
Cluster 3	**testset**	**198**	**55.58 - 936.73**	**27.55**	**17**
Cluster 4	trainset	247	62.64 - 305.56	55.73	26
Cluster 4	testset	85	72.39 - 253.41	80.37	27
Cluster 5	**trainset**	**1194**	**60.06 - 428.17**	**26.39**	**17**
Cluster 5	**testset**	**508**	**58.35 - 373.24**	**24.59**	**17**
Cluster 6	trainset	118	45.44 - 2176.63	61.62	33
Cluster 6	testset	47	50.66 - 1101.37	51.71	31
Cluster 7	**trainset**	**175**	**44 - 441.76**	**47.04**	**32**
Cluster 7	**testset**	**66**	**48.82 - 495.04**	**41.42**	**33**

The MAPE represents how much (in percentage) the predicted creatinine differed from observed creatinine within each cluster. Clusters with low RMSE such as cluster 5, had a relatively low MAPE of 17% which meant that on average, the predicted creatinine was only 17% different from the true creatinine. Table 5.5 shows that some clusters had markedly different error rates from each other. The highest MAPE is 34%, found in the cluster 1 test set, which also contained the least number of patients assigned out of all the clusters.

From these validation tests we can say that our creatinine predictions have between 17 – 34% mean error depending on cluster assignment. However, since the majority of patients were assigned to clusters 3 and 5, those with the least MAPE overall, it can be said that most patients will tend towards the lower error clusters on assignment. We can furthermore deduce from this that the predictive ability between training and test sets were very similar, and so there was little evidence of overfitting.

5.3.6 Generating a prediction

To predict creatinine, we first needed to simulate cluster assignment from new data, then use the model of the assigned cluster to predict the next creatinine value in the set. As a trial, we took patient 1 from the test data and took the following steps:

I. Patient's longitudinal data was extracted and shown to have 61 creatinine measurements spread out over different time points.
II. We took the first 10 time points and hid the rest of the data.
III. We used the trained clustering algorithm to assign this 10-data-point series to a cluster – cluster 5 was assigned
IV. We used the cluster 5 model to predict the 11^{th} creatinine data point.

The result was a predicted creatinine 72.64 umol/L. The real value was 59, showing a difference between predicted and real values of 17 umol/L, within the range of the reported RMSE of cluster 5 of 24.59 umol/L. In this way we are able to simulate prediction of creatinine in new patients to within the defined error margins.

5.4 Discussion

5.4.1 From clusters to renal monitoring guideline

A clustering algorithm has been established, which classifies patients into one of 7 categories based on their individual characteristics. Once assigned, a prediction estimate for creatinine at a future time point can be generated, with an error range specific to that cluster. These properties provide the tools to start developing a provisional guideline for renal monitoring that is truly personalised.

5.4.1.1 Risk Categories

Using the average slope of log(creatinine) change over time for each cluster, each cluster can be labelled as a risk category in and of themselves. The severity of the risk for each cluster would match the direction and gradient of the related slope. This allows us to translate the cluster assignment function directly into clinical terms.

Severity of each cluster can be labelled thus:

- Cluster 1 = severity degree 7 (highest). Time since HF slope = 0.352 (highest)
- Cluster 2 = severity degree 6. Time since HF slope = 0.172
- Cluster 4 = severity degree 5. Time since HF slope = 0.119
- Cluster 5 = severity degree 4. Time since HF slope = -0.012
- Cluster 6 = severity degree 3. Time since HF slope = -0.044
- Cluster 3 = severity degree 2. Time since HF slope = -0.086
- Cluster 7 = severity degree 1 (lowest). Time since HF slope = -0.398 (lowest)

A greater positive change equates to a greater exponential rise in creatinine over time, and thus worsening renal function. Therefore, the more positive slopes are higher risk of renal decline over time and so warrant closer monitoring. The assignment of clusters

can therefore be used to establish the initial monitoring regime per patient, before being personalised further by other individual factors.

5.4.1.2 The prediction of creatinine value

The prediction generated for creatinine value at a given time point depends on the cluster assignment for each patient. Since each cluster acts as its own prediction model, this provides a semi-personalised future projection of each patient's renal health status and supports intervention decisions based on this predictive outlook.

Since the risk severity can be approximated by the cluster assignment, an initial monitoring rate can be set based on the cluster number. The prediction of creatinine will on average follow the slope of the regression line of creatinine over time for that cluster, which determines the direction of change we expect for that patient. This can be personalised further by considering the patient's most recent recorded creatinine. This can be used as an offset value to indicate the level of renal impairment at which the patient starts off, so that when the cluster model is applied at this start point, it gives a more accurate prediction of the creatinine for that patient over time.

5.4.1.3 Using error range as threshold triggers

When a creatinine prediction is generated, the average upper and lower bounds of that estimate is based on the percentage error value using the MAPE for that cluster. For example, a 17% error rate (such as in cluster 5), means that the true value is likely to lie +/- 17% of that prediction. The upper bound of this prediction (i.e. the highest predicted value of creatinine, which relates to the worst renal function outcome) could be used as a marker for potential maximal renal decline. Thresholds could then be set

for this marker, which would be mapped to clinical decision rules, to determine when monitoring frequency needs to be increased. This method takes into account the uncertainty of the prediction, and provides guidance based upon the worst predicted outcome, in order to minimise the risk of rapid renal deterioration. Based on this, it is expected that an initial higher rate of error for patients with less data will prompt further monitoring more frequently. However, as more data is obtained per patient, the error of prediction for that individual may decrease, and if other parameters are stable, the algorithm will recommend less frequent monitoring the more reliable the prediction becomes.

5.4.1.4 Summary of the renal monitoring guideline

To summarise, a clustering algorithm has been generated which can predict data regarding renal function over time for heart failure patients, which could potentially be used to inform clinical decisions on renal monitoring frequency. To utilise this system in new patients, the following process would be used to assign monitoring frequency:

1) *The cluster assignment*

This uses data from the log(creatinine) slope over time, time since heart failure, age at heart failure diagnosis, urea and IMD to give a cluster number at any given time point. This can be used to determine the starting monitoring frequency by matching the cluster slope with severity of renal risk.

2) Most recent creatinine measurement

This can be used to adjust the predictive results from the cluster model to provide a more accurate estimate. It can also be used to fine-tune the initial monitoring guidance provided by the cluster assignment, in the direction of the starting renal function (i.e. worse renal function will have their starting monitoring frequency increased).

3) Deviation from predicted creatinine

Predicted creatinine can be measured as a product of the log(creatinine) model of the assigned cluster, over a set time period. The MAPE can be calculated with the following formula:

Observed creatinine – predicted creatinine / predicted creatinine

As discussed, the MAPE is the percentage error between observed and predicted values, and it can be converted into standard deviations (RMSE). These can be used as a measure of the error of prediction. These outlying values can provide more personalised guidance by modifying the monitoring interval on a case-by-case basis. The worst-case scenario (i.e. highest predicted creatinine) will often be used to trigger established warning thresholds for when to increase or decrease monitoring frequency. This is known as a liability threshold model (Figure 5.20), which would use uncertainty of creatinine value prediction as a measure of risk of renal decline, to guide clinical decisions.

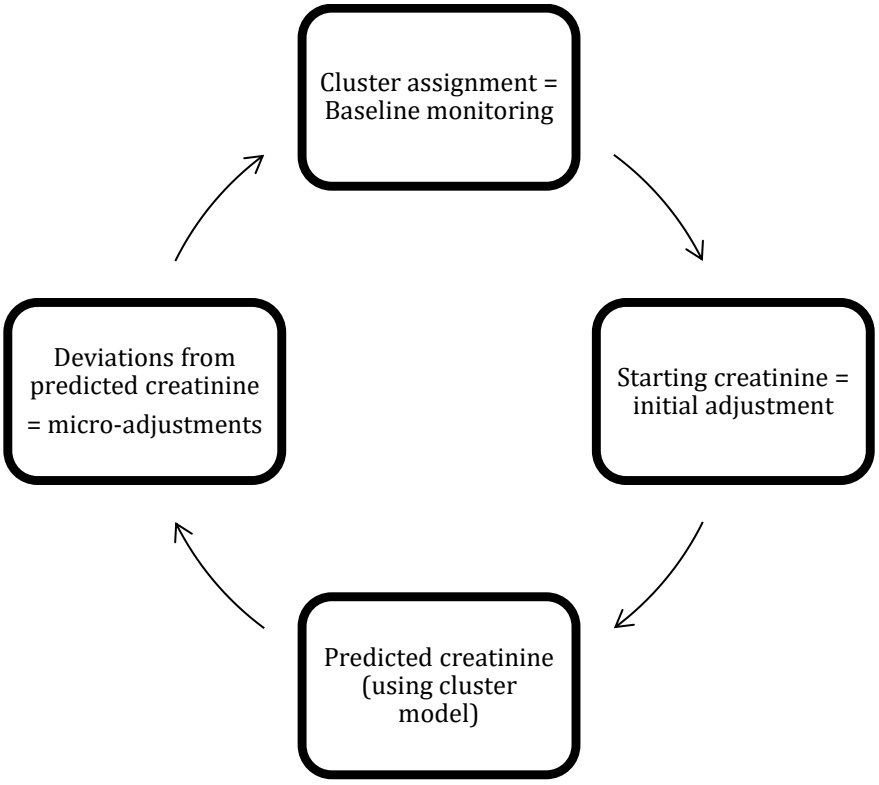

Figure 5.19 Flowchart of the liability threshold guideline using the clustering outputs

5.4.2 Future work required

While we have outlined the general blueprint of the clinical guideline for renal monitoring using the clustering algorithm, there are still aspects which require more work in order to develop this guideline fully, that fall beyond the remit of this project.

5.4.2.1 Using percentage certainty of cluster assignment to personalise prediction

As shown from the posterior probability graph (Figure 5.17), each patient exits in the clustering algorithm with different probabilities of belonging to each cluster, and is assigned to the cluster for which it has the highest probability. Since these probabilities are in flux, and change with each new creatinine measurement, it may be more accurate to consider these clusters as a spectrum, to which each patient belongs to at various

different degrees. Since each separate cluster has its own discrete regression model, it may be that a single model does not match up with the patient's renal profile, especially if they have posterior probabilities close to 50% in multiple clusters.

As an alternative way to adapt this algorithm, the prediction function could be set to take the proportion of probabilities from each cluster, and use that as a weighting measurement for prediction. In other words, each cluster model creates its own creatinine prediction for the patient, and then these predictions are merged with the weight of each prediction mapped to the probability of that patient belonging to each cluster. This creates a much more personalised prediction, using the output of the clustering process for its maximum value, and may be a way to reduce the error rate of each prediction. This also creates a method whereby the predictive algorithm for each patient updates itself and becomes more fine-tuned with each consecutive creatinine measurement, making the most of all the data to improve its accuracy. While this process is theoretical, further experiments with the predictive functionality will be required to assess the stability of this method.

5.4.2.2 How often should renal function be monitored?

To set practical standards for renal monitoring in each case, consideration needs to be given to the possible actions / interventions a clinician might initiate based on the information obtained from the prediction and how long they take to have an effect, as well as the various repercussions of not intervening at the right time. Investigating this use case provides the context in which our guideline would help streamline the clinical process and provide clinical recommendations where they are most needed.

To illustrate the possible clinical interventions that may be possible, it would be beneficial to consider an example case of a heart failure patient who presents to primary care for a routine visit. During the course of this check-up, routine blood screens are ordered, which include urea + electrolytes, a panel which includes creatinine measurement. When the creatinine is found to have risen to >50% of the patient's baseline for the last 12 months, several options are available to the primary care physician at this point. They must first investigate as to the cause of this renal decline, and then trial some interventions to help alleviate the renal burden, and finally they need to re-check the renal function after this intervention to look for improvement. Table 5.6 lists a summary of commonly found reasons for renal decline in primary care and the appropriate actions likely to be taken in the community setting.

Table 5.6 List of investigations and management options for a broad range of causes for renal decline

Aetiology of renal decline	Investigations	Management
Dehydration	Blood tests, clinical exam	Encourage fluids; reduce diuretics
Infection: urine, chest, abdominal, unknown source	Urine tests, chest X-ray, blood culture	Antibiotics
Medication toxicity	Drug history	Withdraw nephrotoxins; reduce dose of medications
Auto-immune causes	Blood tests, imaging, renal biopsy	Steroids; immunosuppressive therapy
Diabetic nephropathy	HbA1c, glucose readings	Diabetic control
Obstructive causes: calculi, prostate, malignancy	Renal ultrasound, bladder scan, cystoscopy	Catheter, nephrostomy
Hypertensive nephropathy	Blood pressure	Blood pressure control
Hyperuricaemia/ Gout	Serum urate	Colchicine, allopurinol, other urate-lowering therapies

In between each of these steps, is a lag effect, which affects the timescale of the disease process. This means that there is a time difference between the cause of the renal decline occurring, and it manifesting in creatinine. Likewise, a time difference occurs between taking the creatinine measurement and the physician seeing the results. Similarly, any intervention will take some time to manifest in the patient's blood chemistry and hence show a response. For the various different causes of renal decline, each of these time courses is different, and it is important to appreciate this fact when constructing time-based guidelines. Any clinical recommendation must allow for the

time taken to undertake the necessary investigations and management in consideration of the time required for the response to manifest.

It is difficult to determine what the lag time is for each patient developing creatinine abnormalities after a renal insult, since this varies between patients and depends on their pre-morbid state and other comorbidities. However, these patients in particular are susceptible to more rapid renal decline than average owing to their pre-existing heart failure. In general, there are acute causes of renal decline, sub-acute causes and chronic causes.

Acute causes are often reversible and severe shifts in physiology that affect renal function suddenly and in a profound way. These include most of the pre-renal causes such as dehydration and sepsis, however they can also be caused by specific medications such as gentamicin or contrast agents, or post-renal obstruction if it is acute. The timespan for acute deterioration is between 1 – 7 days, and this is acknowledged in the KDIGO guidelines for acute kidney injury.[243] With this in mind it is important to consider that the lag time between requesting a blood test and the primary care physician being able to see the result is likely to be up to about 1 week. This means that routine primary care investigations at present are not suited to monitor the clinical status of an acutely deteriorating renal function, and these patients are better managed in a more closely monitored setting such as hospital or satellite clinic.

Sub-acute causes can vary in time to manifest from between weeks up to a year, depending on the instigating cause. Some auto-immune conditions such as systemic lupus erythematosus (SLE) are more chronic, lasting years, however some conditions such as Goodpasture's syndrome can lead to a more rapid renal decline, leading to end stage renal failure over a few weeks. Certain medication can also be included in this

category, again, specific to the type. For example, a high dose of diuretic can manifest within a couple of days with AKI, however, a long-term dose that is too high for the patient can have a slower renal detriment that is only picked up months afterwards with gradually progressive decline, by which time the damage has been done.

Chronic causes are ones that do not cause sudden changes to kidney function, but instead create a structural change gradually over time. This is likely to be prevalent in the entire patient cohort, owing to the presence of cardio-renal syndrome from pre-existing heart failure. In addition to this, poor blood pressure and glycaemic control would contribute to structural changes such as atherosclerosis that reduce the efficiency of the kidneys over time. This takes many years to manifest, but the effect is cumulative and irreversible, and thus poses an inevitable risk in these patients. Monitoring and predicting this risk would therefore go a long way to prioritising interventions and care for these patients, before the signs of irreversible decline manifest. The timescale for CKD diagnosis reflects this as it is calculated while compared to a baseline of 3 months or greater with a stable renal function.[93]

Therefore, keeping in mind the lag time between manifesting renal decline, and the most common causes of renal injury in these patients, the current use case for primary care would be to follow up stable patients with chronic renal decline, and patients at risk of sub-acute decline. The time required to obtain results from blood tests in primary care mean that acute causes of renal injury are difficult to monitor effectively in the community, however the first investigation is useful to highlight patients in need of urgent hospital admission.

We can also conclude that the minimum monitoring frequency we can expect a primary care guideline to recommend would be on a weekly basis. The maximum monitoring frequency within this cohort of at-risk patients would likely be 6-monthly,

which is also the maximal frequency of monitoring recommended by NICE currently for the management of stable heart failure patients.[1] Therefore our clinical recommendations need to cover this range of frequencies when evaluating rate of monitoring for each patient, adapting this to their personalised characteristics. While this is a good starting point for our clinical guideline, the practicalities of these recommendations need to be evaluated during clinical testing.

5.4.2.3 Setting the thresholds for renal monitoring

A critical role for the algorithm is to provide clinical decision support for recommendations of monitoring frequency in this primary care setting. Part of this is the decision of when to trigger escalation or de-escalation of monitoring frequency in response to changes in observed renal function. For this, we need to set thresholds that trigger an accompanying action or recommendations within the clinical setting. These thresholds need to have an evidence base rooted in renal outcome based on observed changes.

Several established categories exist on which to base this on, notably, the clinical criteria used for the diagnosis of AKI, CKD and worsening renal function (WRF). Each of these define specific criteria for the diagnosis of renal decline at different stages of severity. However, instead of making the diagnosis at the time, the clustering algorithm will allow us to project a patient's renal function and estimate at what future time point they may be at risk of reaching the next stage of renal risk. We can then suggest measures to intervene, or increase the frequency of monitoring, before this stage occurs, potentially avoiding the detrimental outcome.

The criteria for CKD uses the eGFR of each patient at any time point and is outlined earlier in this chapter. In contrast, the criteria for AKI and WRF may be more directly translatable from the clustering outputs as they use raw creatinine values, either absolute change or percentage change from baseline, and thus do not need further conversion into eGFR. As mentioned previously, the diagnostic remit of AKI is usually within 7 days of the previous creatinine test which is rare and impractical in primary care, and so it is likely that the WRF criteria is the best suited as a starting point for setting our clinical guideline thresholds at this stage. The accepted biomarker definitions of WRF, outlined earlier in the thesis (Table 1.1), are defined by several different classes, which can be interpreted by either raw or percentage change of creatinine. Furthermore, we need to keep in mind the current error rate of our creatinine prediction. As it stands, the lowest average predictive error (MAPE) was in cluster 5 which still gives +/- 17% from the predicted range. This means that most predictions generated would hit a threshold of 17% change if implemented. In contrast, the highest error found was that of 34% from the cluster 1 test set. If we compare this WRF class 2 criteria of >25% change in creatinine from baseline, we can see that patients in this cluster will always hit this threshold under the liability threshold model. While it can be argued that cluster 1 is the highest severity cluster and thus would warrant extra monitoring most of the time, the same cannot be said for cluster 7, with an error rate of 33%, yet being the lowest severity cluster in the set.

Therefore, our initial thresholds, while keeping the evidence base in mind, need to respect the limits of the algorithm's predictive ability and create a suitably flexible clinical decision system that can leverage this to its fullest. It may be that using a set of thresholds unique to each cluster would be the best solution so that the uncertainty of the prediction can be standardised across each patient in this way. At this point,

further work needs to be carried out to establish these thresholds and testing the most effective decision system in a clinical setting is essential for this.

5.4.2.4 Implications for clinical practice

In practice, the way the algorithm is intended to be used would be within the primary care setting, at the decision point of how frequently to monitor the heart failure patient's renal function. With a fully optimised algorithm, it would be able to predict future creatinine values, using only the patient's retrospective urea, creatinine and demographical data. The algorithm would need at least two previous creatinine measurements from the same patient in order for a cluster assignment to be made. However, the accuracy of that assignment, as well as that of the predicted creatinine values would be greater the more retrospective values are available. This is a potential drawback of the algorithm in that with little retrospective data, the cluster assignment may not fit initially, however its performance increases over time. This may result in higher error margins and recommendations of greater frequency of monitoring at the first instance, before the pattern of renal change can be fully recognised and stabilised by the algorithm.

5.4.3 Limitations

In the process of creating this predictive model, there are a few limitations that need to be considered before its use is put into practice.

5.4.3.1 *Incident heart failure cases*

The patients in this cohort were all ones who were recently diagnosed with heart failure, since their date of diagnosis had to fall within the study window for them to be included. For this reason, the algorithm trained on this subset of patients may not be applicable for patients with who have had chronic heart failure for >5 years, since the mean follow up time for this study was less than 3 years. It may be that longer study windows are required in order to adapt the algorithm to longer-term sufferers of heart failure.

5.4.3.2 Assumptions of the clustering model

The current clustering algorithm requires several assumptions to be made which may have an impact on the prediction performance. In the first instance it assumes that all covariates included in the model are independent with minimal overlap and co-linearities. Due to this, it is unable to include more complex renal covariates such as eGFR and WRF which overlap with creatinine. Furthermore, the model assumes a Gaussian distribution, and we have demonstrated that log(creatinine) fits this pattern. However, the implication for the algorithm is that this would require conversion of raw creatinine to log(creatinine) before cluster assignments can be made, and re-conversion into raw creatinine for the prediction value. Finally, there is an assumption that each patient within a cluster acts in the same way over time. It has been shown that patients may not always have 100% posterior probability to one cluster and may be a combination on multiple clusters. The implication is that this may increase the error of prediction for those patients that do not completely fit into their assigned cluster. As the certainty of the cluster assignment improves, the predictive

performance may do so as well, however this would require more retrospective data, which would take more time to obtain.

5.4.3.3 *High predictive error rates*

As eluded to earlier, having an error rate for prediction over 33% likely means that whatever threshold of percentage change over time we instigate within the guideline would be limited to values above this percentage change. This therefore excludes us from including more sensitive thresholds such as the criteria for WRF stage 2 which marks percentage change >25% as a trigger. Without improving the precision of the prediction itself, we cannot introduce more robust and sensitive thresholds into the guideline.

5.4.3.4 *Unsupervised learning*

As mentioned in the introduction, a criticism of many machine learning methods is the 'black box' element of its design. While clustering is not as impenetrable as deep learning methods such as artificial neural networks, it still involves an element of machine-directed optimisation, over which the user has little control. To allow for this, we ran the model in a multitude of cycles until we obtained the most stable explanatory model. This does little to explain how the model arrived at its present state, however, we have the tools to conduct repeat studies, and we expect that similar results can be obtained and replicated using the same data, with the information provided within our methods. Furthermore, the model-based outputs of each cluster use a regression framework, which allow us to have a clear-cut interpretation of the relationship between variables. This makes it possible to observe the associations generated by the

algorithm for each cluster, making the outputs much more transparent than other 'black box' methodologies.

5.4.4 Conclusion

This study has been an important step in the generation of future clinical guidelines for renal monitoring in heart failure patients. We have shown how, using large clinical datasets, a clustering model can be trained to predict future creatinine. The methods used here may be an important pre-cursor for future studies looking at the predictive value of clinical datasets and attempting to create personalised guidance for heart failure or other chronic conditions.

While the sample size was greatly reduced by our inclusion criteria, and limited by the size of the dataset provided, it created a very homogenous cohort for us to test our concept. Further trials on larger datasets using this method are therefore likely to yield a more robust predictive algorithm which would strengthen future guidelines generated by this. In addition, there are numerous optimisations that can be tested in regards to the prediction calculation. This would help reduce the range of error, improve the personalisation of the guidance, and increase the sensitivity of the thresholds that can be used.

While it may be that the eventual guideline recommends further monitoring in patients than is current practice, it will perhaps pave the way for remote care technologies to have a role in the chronic management of heart failure patients. Frequent and non-invasive monitoring in the patient's home setting may generate a rich enough data that predictions with error rates much lower than reported can be achieved and allow us to prevent hospital admissions with greater efficacy. Furthermore, a more rapid interface

time between requesting tests and observing the results remotely will reduce the lag effect in primary care monitoring. This will allow us to advance the use case of this algorithm to cover more acute causes of renal deterioration and monitor patients pre-AKI, observing and adjusting advice in response to daily changes. This will create an added measure of safety for these patients and a greater level of personalisation, using future advancements in technology to improve the predictive process and potentially reduce morbidity. Further work is however needed in this regard, both in defining the guideline and in clinical trials within a practice setting, and this will be detailed in the following chapter.

CHAPTER 6

DISCUSSION

CHAPTER 6: DISCUSSION

6.1 PERMIT Project Summary

6.1.1 The gap in clinical guidance

The PERMIT project has aimed to bring current medical knowledge closer towards the creation of personalised clinical guidelines for monitoring renal function in heart failure patients. This gap in clinical guidance, as well as its implications, has been highlighted in detail in chapter 1, the contents of which have subsequently been published as a narrative review in the British Journal of Clinical Pharmacology.[340] It found that much of the existing guidance is based on expert opinion, and that very few studies have examined the optimal frequency of renal function monitoring in patients with heart failure. This has led to a widespread variance in practice, which is non-standardised and reliant on individual clinical judgement. A personalised approach to guidance offers a potential solution, by standardising practice and safe management for this vulnerable patient cohort.

6.1.2 Investigating factors that affect patient and clinician engagement with remote care

To pave the way for personalised predictive monitoring, it was necessary to explore the experiences of patients and clinicians when engaging with medical technology already in use for heart failure care. A qualitative systematic review was conducted to identify overarching themes from user experiences, in order to better design future remote care technologies. It was found that the themes of engagement with remote technology centred around ‘convenience’, ‘clinical care’, ‘communication’, ‘ease of use’, and ‘education’ (Chapter 2). These themes were generated by looking at published qualitative primary studies and applying thematic analysis to interpretations and documented user feedback.

6.1.3 Discrete choice experiment into patient engagement with technology

To obtain prospective patient-facing data regarding these attributes of remote care technologies, and to try to quantify the relative value of each to heart failure patients, a discrete choice experiment questionnaire survey was designed. The questionnaire asked participants to weigh up the different attributes against each other in each choice. Based on the results using binary logit analysis, the attribute of 'clinical care' i.e. that a remote care technology significantly improved clinical care, was the most valued attribute. Specifically, it was nearly twice as important as communication, the lowest ranking attribute, and would often be traded for any two other attributes of the five that were assessed. This is an important finding as it shows the priorities for patients in terms of engagement with technology design.

6.1.4 Studying a heart failure population group

In order to create the predictive clinical tool, large clinical datasets were required to identify the characteristics of heart failure patients and map their renal function progression over time. Access to Salford Integrated Records data was obtained, which contained data on a group of patients with heart failure living in Salford, over a study window of 8.5 years. This was a patient cohort of newly diagnosed heart failure patients that were predominantly Caucasian, and lived in areas with high deprivation levels. Analysing the progression of creatinine over time within this cohort showed significant correlation with serum urea and potassium levels. In addition, loop diuretics were the most strongly linked medication category to creatinine progression over time.

6.1.5 Creating a machine-learning predictive tool

In order to design a decision tool that would be flexible for each patient, a machine learning approach was considered to be a potential solution and a pre-cursor to future personalised guidance. Having analysed this patient cohort, various methods were trialled to apply machine learning into this longitudinal dataset and obtain a predictive model. A clustering methodology known as 'flexmix' was compatible with the constraints of our clinical dataset and practical enough to be used within the timescale of the study. Further analysis of the data showed that serum urea had the highest R-squared value in explaining creatinine variance over time, outperforming the other clinical correlates to creatinine. We therefore chose a predictive model which used fixed covariates of age at heart failure diagnosis, time since heart failure diagnosis gender, IMD, and serum urea. Two-thirds of the data were split to train the clustering algorithm and one-third was kept for testing and validation. After the clustering process was complete, we ended up with 7 discrete clusters of patients. There was a high rate of posterior probability shown in the test set, which meant that the cluster assignments were accurate. The model eventually was able to yield a predictive creatinine value with an average error rate between 17-33%, depending on the cluster assigned.

6.2 Future work planned

While the foundation for the predictive model generation has been established in this study, there are further steps to take before it can be viable as a practical application.

6.2.1 Additional data

The original project outline included adding data from the Clinical Practice Research Database (CPRD), a much larger dataset which covers around 1700 GPs nationally, and contains data on up to 180,000 heart failure patients. While the processing time and additional analysis steps of this were beyond the time-scale of this project, this CPRD data has already been obtained for the purpose of this future work. It is envisioned that running the same methods and techniques that have been explored in this study in this larger sample size will optimise the accuracy of prediction and create a more robust algorithm that can be more widely applied. It also provides a wider range of patients with heart failure across the UK and may create additional or more specific clusters to categorise the risk for these patients.

6.2.2 Optimising predictions

While the error rate obtained in this study was relatively high, there are various avenues available to personalise and structure this more around each patient and increase the effectiveness of each individual prediction. Certainly an offset function that takes into account the patient's previous creatinine values can be added to the prediction algorithm to make a more accurate estimate. Furthermore, as discussed in chapter 5, there may be other optimisation parameters that can be found by interrogating the test data more thoroughly, and this is best done after clustering in a larger dataset so that high sample clusters are used for maximum efficiency.

6.2.3 Decision support rules

An initial frequency of monitoring can be set according to the cluster assignment based on risk severity. Monitoring can then be fine-tuned by using the previous creatinine of each patient, and then the error of prediction will guide whether to increase or decrease monitoring over time. When the effectiveness of the algorithm prediction has been optimised it will allow the use of more sensitive thresholds for monitoring in heart failure patients. This clinical guideline will be optimised for heart failure in the first instance, but there are many other diseases where renal function declines, such as in diabetes and hypertension, where adaptation of the monitoring schedules developed here could be useful.

6.2.4 Prospective clinical trials

In order for any new clinical guideline to be accepted, it needs to be validated in a prospective trial to evaluate its acceptability and benefit to clinical care. As we have seen, the proven benefit to clinical outcomes goes a long way to increase engagement towards the intervention, both for patients and clinicians. The benefit of a personalised renal monitoring system is that it would provide a means for intervening before rapid renal decline, and therefore prevent avoidable hospital admissions in patients who are at risk. Therefore, potential outcomes of clinical trials can include reduction in hospital admissions and AKI episodes while using the new guidance. This may require a long term follow up study of a number of years before the outcome data can be used for validation purposes.

6.2.5 Incorporating guidelines into clinical practice

As explored in our qualitative review, integration and acceptance of new disruptive technology has obstacles, and therefore, future integration into clinical care should be underpinned with implementation science methods.[341-343] The renal monitoring guideline is envisioned to be a system that sits side-by-side to primary care electronic health record (EHR) systems. It would thus able to draw data from patient records and report recommendations automatically, using the information systems that are already established. To facilitate this, preliminary discussions with the providers of the EMIS system, which is one of the main health record systems in UK primary care, have been held. Clearly, this will require additional support from electronic health companies or modular systems that are already in use. The insight gained from this project into the factors that encourage engagement will likely aid the design of an acceptable interface that is valued by both clinicians and patients alike.

6.2.6 Future Opportunities in remote care technology

The plan for this guideline was drafted with the advancement of medical technology in mind. To this effect, new remote monitoring devices that can be used to measure renal function parameters in the community should be considered in the future. The use of remote care has the potential to provide great benefit both in clinical care and patient safety, and it incorporates well with our machine-learning methods. Further work will need to be done in the future to determine where in the community such monitoring can take place (for example, could it be done in a patient's home, or would it be best placed in a high street pharmacy or GP practice). Clearly, an environment rich with more frequent data points will allow us to optimise our predictive ability per

patient and will also allow us to broaden the range of recommended monitoring frequencies to include more acute cases, such as multiple-day monitoring regimes.

6.3 Conclusion

This project has explored the potential of creating a machine learning predictive model for clinical purposes. The initial narrative review has identified deficiencies in the guidance and evidence around monitoring of renal function for heart failure, which prompted our efforts to create a predictive model for this. It was determined with some success that prediction of future renal function is possible using large clinical datasets. This can be personalised further and eventually lead to patient-based advice on monitoring of renal function in a heart failure population. As mentioned, more work needs to be done to solidify the guidance as well as improve the prediction parameters, however, this preliminary work is an important first step as a proof of concept of machine learning methods in clinical design. It is likely that future studies may use similar methods to create their predictive models from clinical datasets, and this may lead to personalised guidance in other medical conditions.

This project has also helped to explore the experiences of engagement with medical remote care technology for heart failure patients. The qualitative systematic review led to the generation of 5 central themes which were adapted into a discrete choice experiment. These efforts generated a hierarchy of important technology factors for user engagement. This ties together the vision of using remote care technology and predictive analytics together to create a more personalised primary prevention guideline for heart failure care. Since our predictive accuracy increases with the frequency of monitoring and richness of data, remote care may be a critical asset for

applying flexible monitoring schedules for patients with chronic disease and a lack of independence and mobility.

In the current clinical climate, it is projected that remote care will become an ever more vital part of the way healthcare services are distributed, and work into the factors that improve its uptake will be important for future technology advancement in the field. Coupled with manipulation of big data for health outcomes, personalised digital medicine can transition our health strategies from being reactive to being proactive, in order to prevent poor clinical outcomes. This study helps to pave the way towards this transition by highlighting the potential of machine-learning led guidelines and bridging the gaps between these clinical decision support systems and technology implementation in heart failure patients.

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APPENDIX

APPENDIX 1: SEARCH STRATEGY FOR NARRATIVE REVIEW ON RENAL FUNCTION MONITORING GUIDELINES (CHAPTER 1)

Database: CDSR/Central/ DARE/HTA

#1	MeSH descriptor: [Heart Failure] explode all trees	6571
#2	MeSH descriptor: [Edema, Cardiac] explode all trees	22
#3	MeSH descriptor: [Heart Failure, Diastolic] explode all trees	31
#4	MeSH descriptor: [Heart Failure, Systolic] explode all trees	143
#5	((heart* or cardiac* or myocardial* or ventric*) near/2 (fail* or decompensat* or insuffic* or dysfunc*))	20023
#6	#1 or #2 or #3 or #4 or #5	20032
#7	MeSH descriptor: [Glomerular Filtration Rate] explode all trees	2203
#8	(glomerul* filtrat* rate*)	5129
#9	#7 or #8	5129
#10	#6 and #9	605
#11	time or frequenc*	260059
#12	#10 and #11	234

Database: Medline

Strategy used:

1	heart failure/ or edema, cardiac/ or heart failure, diastolic/ or heart failure, systolic/	99711
2	((heart* or cardiac* or myocardial* or ventric*) adj2 (fail* or decompensat* or insuffic* or dysfunc*)).tw.	175303
3	1 or 2	201910
4	glomerular filtration rate/	37180
5	(glomerul* adj1 filtrat* adj1 rate*).tw.	34172
6	4 or 5	52142
7	3 and 6	2543
8	animals/ not humans/	4271460
9	7 not 8	2378
10	(time or frequenc*).tw.	3071275
11	9 and 10	339

Database: Embase

Strategy used:

1	heart failure/ or edema, cardiac/ or heart failure, diastolic/ or heart failure, systolic/	178169
2	((heart* or cardiac* or myocardial* or ventric*) adj2 (fail* or decompensat* or insuffic* or dysfunc*)).tw.	256795
3	1 or 2	304803
4	glomerular filtration rate/	44915
5	(glomerul* adj1 filtrat* adj1 rate*).tw.	43628
6	4 or 5	63953
7	3 and 6	4753
8	animals/ not humans/	1172721
9	7 not 8	4734
10	(time or frequenc*).tw.	3740110
11	9 and 10	748

Database: Web of science

Strategy used:

TITLE: ((heart* or cardiac* or myocardial* or ventric*))*AND* TITLE: ((fail* or decompensat* or insuffic* or dysfunc*)) *AND* TOPIC:(glomerul* filtrat* rate*) *AND* TOPIC:(time or frequenc*)

Database: CINAHL

Strategy used:

1	CINAHL	exp HEART FAILURE/	19918
2	CINAHL	(((heart* OR cardiac* OR myocardial* OR ventric*) adj2 (fail* OR decompensat* OR insuffic* OR dysfunc*))).ti,ab	24727
3	CINAHL	1 OR 2	30876
4	CINAHL	exp GLOMERULAR FILTRATION RATE/	3584
5	CINAHL	((glomerul* adj1 filtrat* adj1 rate*)).ti,ab	2894
6	CINAHL	4 OR 5	4861
7	CINAHL	3 AND 6	400
8	CINAHL	(time OR frequenc*).ti,ab	273088
9	CINAHL	7 AND 8	49

APPENDIX 2: STUDY PROTOCOL FOR SYSTEMATIC REVIEW ON FACTORS AFFECTING ENGAGEMENT IN REMOTE CARE (CHAPTER 2)

INTRODUCTION

Heart failure is a major cause of morbidity and mortality and is a growing problem in the UK, affecting up to 900,000 patients. These patients have an average age of 76 and the prevalence of heart failure increases with age.[1] They have reduced mobility, cognition, mood and often have 3-5 severe co-morbidities including diabetes mellitus, COPD, and ischaemic heart disease.[2] One year mortality rates for these patients are as high as 40%, and 30-50% of these patients are re-admitted to hospital each year due to worsening of the disease condition.[3] Self-care and efficacy issues prevail in the management of these patients, compounded by aspects of other co-morbidities as well as the complex nature of their management and poly-pharmacy.

New remote-care technologies have been developed to work with patients to support their self-care behaviours, making their health condition easier to manage for themselves. The assumption behind the development of these technologies is that by allowing the patient to gain control of their own health, severe health issues may be identified and steps taken to resolve these early, before the patient requires hospital admission. This both improves the quality of life of patients and reduces the burden of disease on healthcare services.

This review is aimed at exploring these new complementary remote distance technologies, in particular, the effect these technologies have on patient's engagement with their care. However these technologies would not be available nor accessible to patients if not for the initiators from the healthcare providers. Therefore this review will cover the factors affecting technology engagement from not only the patient but also the practitioner perspective.

In so doing, the review will aim to identify key themes and issues which need to be explored during future integration studies of these new technologies. Consideration of these key issues in design and integration will then help to both increase acceptability and retention of the intervention with patients and healthcare workers; a patient-centred approach to implementation.

Description of the phenomenon of interest

Remote care is a term used to encompass devices and technologies which allow health-care and disease management strategies to be applied outside the confines of a clinical setting, be that at a patient's home or pharmacy or another communal institution such as residential homes.[4] This also includes interfaces and sources of information that can be accessed from the comfort and convenience of the patient's home or workplace. In essence, any intervention which can offer the same kind of advice and information that a patient would receive when visiting their healthcare practitioner, without physically being within the clinical setting is designated as remote care.

Examples of this include devices in the home which measure clinical parameters which are then fed back to clinicians, often referred to as home-monitoring or tele-monitoring

systems.[5] Other examples involve regular structured telephone conversations with the patient to provide information and advice about self-management for complex medical conditions.[122]

Heart failure is one such complex condition and has potential to benefit greatly from these remote care technologies. It includes a patient cohort which is burdened with severe co-morbidities, reduced mobility which can impair access to health services, and debilitating symptoms which can limit daily activities. In these patients, where travelling to clinical settings can be an issue due to clinical symptoms as well as social circumstances, remote technologies have found a niche. As with similar chronic conditions, several technologies have been designed to aid self-care behaviours, and to provide regular monitoring for patients which need it, bridging the gap between clinical visits.[122]
This review will focus on those remote care technologies centred on improving, and contributing to, the management of heart failure patients. In this context, the phenomenon of patient and healthcare engagement with the technology will be studied, drawing on experiences, barriers and facilitators to increasing engagement with these interventions.

Why is it important to do this review?

Whenever a new remote technology is trialled in healthcare settings, obstacles for implementation are soon encountered. Most significant of these is the extent of engagement and acceptability the intervention has from both the patients it is intended to assist, and the practitioners involved in its administration.

The issue of non-adherence is an increasing problem in this patient group, not only with new technologies but in the daily medical management of their chronic condition also. Up to 65% of hospital admissions in heart failure patients can be attributed to poor adherence with treatment regimens.[7] Serious complications related to non-adherence are prevalent because their medical management is often a careful balancing act between clinical symptom control, and severe adverse effects such as hypotension, dehydration, and renal failure. The complexity of the condition, coupled with a number of other serious co-morbidities, mean that self-knowledge and adherence with all medical measures becomes akin to a full-time occupation. Self-management strategies need to be employed to increase the independence of these patients to prevent deterioration. However In an elderly population with decreasing cognitive ability and mobility, the obstacles relating to patient engagement become that much greater.[8]

The drive and enthusiasm to try novel interventions can quickly fade away without physician support. Healthcare practitioners may feel disheartened with the lack of engagement of their patients leading to a lack of motivation to trial new technology in their patient's care. Therefore the acceptability of technology towards clinicians and healthcare providers needs to be equally explored.

Evidence for effectiveness of new technologies is often conducted through clinical trials of a short duration, in uncomplicated patients, and with a dedicated clinical intelligence and implementation team. In practice, such novel interventions require a continued drive from both patient and practitioner in order to be sustained through the management of complex chronic conditions over the longer-term. [9]

Implementation of remote technologies, without consideration of patient and practitioner engagement factors, are likely to see a steep decline in retention once the initial enthusiasm expires.
To avoid this, and to increase engagement for future remote care technologies, perspectives and opinions need to be considered from the patient-view outwards. This review seeks to gather qualitative evidence which identifies the most prevalent factors that influence patient adherence with remote care technology. In addition, we will also explore the published perspectives of healthcare practitioners for factors that affect engagement and promotion of new technologies for management of their heart failure patients. This ensures a greater understanding of the personal impact of technology on chronic conditions, both on patients and implementing staff.

Understanding the factors identified in this review will have important implications for the research, design, and implementation of future remote care technology. Firstly, considering factors affecting patient adherence, allows new technology to be designed around the patient's needs and utility, increasing its impact on their lives. Considering physician engagement allows user interface between technology and physician to be streamlined such that the most vital clinical information can be tailored to the needs of the clinician when it is needed most, to speed up the process of monitoring and diagnosing their patients. Furthermore identifying personal issues leading to a compliance decision in this way provides a framework for future trials of remote care technology to assess the personal impact of technology on patient lifestyle and likelihood of sustainability. Therefore these factors are important in the design of clinical trials for remote care as well as the design of the technology in itself.

In any new intervention implementation there is an unavoidable disparity in healthcare provided between early adopters and lagging practices as they take time to implement the new process. This creates a health inequality due to a difference in the health service provided. Often, this inequality is impeded further by location or socio-economic factors. These health inequality 'gaps' have been implicated in the worsening health outcomes of lower socio-economic groups.[3]
In exploring the themes relating to engagement, it is expected that we will encounter factors relating to patient accessibility and barriers to dissemination of new interventions. In this review, we aim to discuss the differences in area and social status of population within studies to look at differing levels of acceptability and engagement. In this way may be able to evaluate whether there are any related themes to engagement, which may be addressed in future research in order to minimise this widening health inequality brought on by new remote technologies.

Objectives

The review has the following six objectives:

- To Identify, appraise and synthesise qualitative research evidence on factors identified as having an impact on patient engagement regarding the use of remote care health technologies to aid with the management of heart failure

- To identify, appraise and synthesise qualitative research evidence relating to engagement of healthcare staff in the application of remote care technologies for the management of heart failure patients under their care

- To identify, appraise and synthesise potential health inequalities brought about by introduction of novel technologies

- To identify hypotheses and schema from this synthesis for future consideration in the design, development, and implementation of novel remote care interventions to improve uptake and sustainability

- To identify hypotheses for consideration in the design of future clinical trials and feasibility studies of novel remote care interventions

- To identify and develop hypotheses for consideration in the distribution and application of future interventions in order to minimise the health inequality created by them

METHODS

Electronic searches

We will search the following databases for relevant publications and studies published after 1990.

- EMBASE
- Ovid MEDLINE (with in-process and other index publications)
- Pubmed
- Cochrane library
- Scopus

In addition, we will search the reference lists of all included studies for relevant publications.
Appendix 3 shows the full search criteria used for the EMBASE database.
The CINAHL database was excluded due to its low number of relevant included journals and preliminary searches which indicated minimal relevant publications matching our search criteria.

Types of included studies

We will include primary studies which use qualitative methodologies to collect data (e.g. focus groups, interviews) and analyse data (e.g. thematic analysis, grounded theory).
To differentiate qualitative from quantitative surveys in the literature, we will define a qualitative study as one which involves the participant to enter free-text comments or answer an open question. Therefore surveys based on scoring criteria or measurement scales alone will not be classified as qualitative methodology and will be excluded.
We will also include studies with English abstracts only.

Types of Participants

Patients:
Patients diagnosed with adult chronic heart failure. Definition of heart failure is to be determined by clinical criteria in use by each individual study parameter. We will include patients of all severities of disease.

We will exclude studies based on patients with congenital causes of heart failure or cardiomyopathy and paediatric heart failure. Other exclusions which deviate from the definition of chronic heart failure include acute heart failure, isolated pulmonary artery hypertension, acute coronary syndrome and hypertension, and studies focusing on these will be excluded.

Practitioners:
All healthcare staff who are involved in providing healthcare services to heart failure patients (i.e. physicians, specialist heart failure nurses) and who are involved in the use of remote healthcare technology.
All other staff members involved in the delivery, assessment, implementation or interpretation of a remote care technology or programme within healthcare settings (i.e. administrative staff, information technology staff, engineers, managerial or supervisory staff).

Settings
We will include studies of remote care programmes in primary, secondary and tertiary settings as well as in community care settings. We will include studies in both public and private healthcare facilities and we will include studies conducted in any country.

Intervention
For the purpose of this review, remote care programme is defined as any intervention or information source, accessible from the patient's home or environment, which provides the patient with knowledge, assessment, investigation results or otherwise replaces a service which would normally be offered within a formal clinical setting.
Each remote care intervention must be a novel way of providing an existing service in a remote fashion and should not be part of an already existing established care pathway. Therefore current established interventions for heart failure and associated co-morbidities would be excluded. These include long term oxygen therapy (LTOT), cardiac rehabilitation, and any self-care or disease education given at the point of contact in a clinical setting.
Remote care interventions must also be of potential use to all heart failure patients without excluding certain groups. For this reason, our definition of remote care would exclude interventions which affect, track, monitor or otherwise interact with implantable medical devices. Since these interventions are only available to a certain subset of patients with severe end stage disease, they are prone to selection bias compared to other interventions which are usable by all patients
Implantable devices are also a special case in terms of the fact that the patient cannot choose whether to 'engage' with the technology or not since the monitoring of such devices will occur without the patient's knowledge or will. Therefore it is not reasonable to assess engagement with an embedded device in the same way as a mobile application or web service where the user can choose to engage with or not.
Examples of services which would be considered as remote care technology include, telemonitoring services, remote consultations, mobile apps tracking health status, and patient-directed online education programs.

Phenomena of interest

The phenomena of interest are two-fold;

- The factors which go into the patients' decision to adopt, engage and continue to use the remote care intervention for the purpose of self-management of heart failure.

- The factors which contribute to the level of engagement of clinical and non-clinical staff in the implementation of a specific remote care intervention for the management of heart failure

DATA COLLECTION AND ANALYSIS

Selection of studies

The process will comprise the following steps:

Assess abstracts and titles according to inclusion criteria
We will merge the bibliographic details from each electronic database search into one database, and remove any duplicates. The abstracts will then be checked for eligibility with the inclusion criteria. The eligibility criteria will first be discussed and calibrated between two authors (AA and JD). A random sample of 30% of the abstracts will be screened independently by the two reviewers. Disagreements will be resolved by consensus between the two reviewers, following which, one of the reviewers (AA) will continue to screen the remaining abstracts for eligibility using the double-screened sample as a foundation.

Asses full text according to inclusion criteria
Full publication of studies identified in stage one will be obtained and independently assessed by two reviewers. Any disagreements that cannot be managed by consensus will referred to a third member of the review team. If required, we will contact study authors for further information regarding the study details needed to make a decision regarding the inclusion of a study in the review. Included full texts will have their references extracted and these will be screened against the same eligibility criteria and de-duplicated. The remaining texts will be added to the full text inclusions to comprise the final list of included texts.

Potential sampling from the included studies
Due to the nature of the qualitative methods data analysis, a variation in concepts and ideas is required rather than an exhaustive sample of studies. Therefore to allow the greatest extent variety of studies to be included in the analysis, if the number of eligible studies exceeds 40, this review will use maximum variation purposive sampling to select from the included studies. Variation factors will include type of remote care intervention used, location of study, data analysis methods employed, data collection methods used, and primary phenomena examined. Once these have been defined for each publication, a sampling framework will be used to categorically map studies from each variation factor in order to select the broadest range of studies. Once all studies have been mapped, the authors will discuss and reach a consensus on the sufficient number of studies required from each variable to be selected based on the range of variability and number of available studies. The selection process will then take place using the selection framework to cover all variability factors.

Data synthesis methodology: Thematic synthesis

We will be guided by the thematic analysis model of qualitative evidence synthesis in this review.[10] The reason for choosing this model is as follows:

- The review questions and priorities are focused around identifying factors and variables which are major components of patient decisions for adoption, engagement, and retention of remote care technologies. Thematic analysis therefore lends itself well to identifying these variables, labelling the themes extracted from previous research and building upon them to generate a workable theory.

- Thematic analysis identifies a series of comprehensive themes from the synthesis of findings from multiple qualitative research studies to identify a phenomenon. In turn these can form the foundation for recommendations for the implementation of future interventions in the field. Thematic analysis is therefore a very appropriate method of analysis when designing new policies and practices, as is the case in the emergent field of remote healthcare technologies.

- The analytical method is transparent and the outcomes retain the contextual meaning of the original included studies. The benefit of this is in its application for future research and interventions whereby the reader is at liberty to assess whether the context of included studies are relevant to their specific applications. This ensures the review will be as relevant as possible, while being faithful to the original findings of the included studies. In other words, the translational aspect of the synthesis can be easily followed and traced back to the point of relevance for a wider range of utility.[11]

- Alternative methods of synthesis were considered for this review, notably, framework synthesis or 'best-fit' framework analysis.[12] However, while these methods are also useful for generating a workable model for future intervention application, they are reliant on a pre-existing a priori model of the same phenomenon to aid initial data extraction. A scoping search of the phenomenon showed no relevant qualitative review frameworks which address the review question in the form of a model. The authors felt that while the phenomenon of patient adherence is well studied, the context of new remote technologies in heart failure care are specific enough to warrant their own model criteria, and therefore models using generic patient engagement in different contexts were not suitable. Since there are relatively few models or frameworks published in this area, it is inappropriate to adopt an a priori start point. Hence, for the application of future interventions and research, thematic analysis was thought to be the best approach.

Developing data extraction form

The first part of the extraction would involve extracting the study characteristics of included studies (see 'Characteristics of Studies' below for a list of characteristics).
Due to the difficulty of differentiating between primary study findings, author interpretation, and key findings of included studies, an unstructured approach will be taken to the initial results data extraction. The review will treat all text found within the 'results' or 'findings' sections of included publications as extractable data, including those found within abstracts. This textual data will be extracted verbatim using specialised software designed for qualitative data analysis: EPPI-Reviewer. This process will be done by the first reviewer and subsequently cross checked by a second.

Coding textual data

Coding of the extracted text will occur using line-by-line coding techniques, whereby each relevant sentence is interpreted by the reviewer and summarised into a common code or

theme, which it is then linked under. Codes are generated inductively from reading through the extracted text. The purpose of each individual code is to capture the meaning of the text sentence and also encapsulate a general concept to which similar statements and sentences can be linked under. This is predicted to generate a large list of initial codes which summarise the key data findings of included publications, with minimal interpretation or translation.

Generating descriptive themes

From the initial summary codes, similarities and parallels are expected to emerge. Commonalities within each of the codes are then further summarised into more generalisable themes, which act as general description headings of the initial codes. This process of compacting the initial information into general themes gives a birds-eye view of the relevant findings. Additional definitions and descriptions will support each of the themes for clarity, based on the codes they are drawn from. These themes and their relation to the initial codes can then be mapped in a visual way to allow for critical analysis and transparency. At this stage, descriptive themes remain a construct of the initial data extraction and therefore are a close reflection of the findings of the original studies.

Inferring answers to review questions

Our review's focus will be on identifying factors which have an impact on patient and physician engagement. To facilitate this, descriptive themes become our basis for theory generation. Since data extraction is unstructured, our descriptive themes will fit closely to the findings and intentions of the original studies they are extracted from. What follows will be a gradual translation into the question our review is designed to address; namely, what factors of a remote technology have the most impact on engagement, and what the implications are on technology design. The answer to these can be inferred from the descriptive themes generated. It may be that the included publications related very closely to this question, in which case the descriptive themes would directly answer the question in and of their own. However, in qualitative synthesis, the form of descriptions cannot be predicted and therefore, should the descriptive themes deviate from our review focus, our aim would be to take the descriptions generated and clearly define the variables impacting engagement which have been implied by the primary findings.

Generating analytical themes

Carrying this process forward, the translation of descriptive themes into analytical themes occurs. The purpose of further translation into analytical themes is to generate an abstract model or concept which encapsulates all the descriptive themes and inferred constructs into a succinct and applicable model. Analytical themes are designed to be abstract theoretical constructs which are general enough to capture all previous findings regarding the investigated phenomena. Initially, themes will be generated by each author individually, then discussion and consensus will finalise the complete list of analytical themes used. These themes are then brought together into a workable model, which is tested on the included studies for validation. The model is refined and re-tested in this way until it fully explains the phenomena and includes all aspects of the descriptive themes generated previously.

Considering implications for future interventions

Going beyond the findings and explanation of the phenomena of engagement in remote care technology, the finalised model and analytical themes are then used to consider future impact and implications of the research. In this case of this review, we will focus on future intervention design, feasibility study design and clinical trials of remote care technology. The model will provide a robust framework with which to suggest considerations to address in each aspect of technology design and research in regards to patient and physician engagement. This will form the backbone of the discussion as the result of a fully translated model of factors which affect patient compliance. The end result will be recommendations derived from our working model which can be easily applied to future areas of intervention and its related clinical study.

Study Characteristics

Assessment of the study characteristics allows the study findings to be put into context, and helps with the purposive sampling of included publications. Characteristics of study to be extracted will follow the format recommended by the ENTREQ statement,[13] which outlines guidance on reporting of quality synthesis reviews. Where interviews or focus groups took place in an included qualitative study, the characteristics of the study were extracted with guidance from the consolidated criteria for reporting qualitative research (COREQ)[14], which outlines key aspects of reliable qualitative study to be reported on.
In line with our aim to highlight the health inequalities between studies, our population sample data extraction will be broken down as per the PROGRESS framework. This has been widely used as a tool to report on disparities in population samples in systematic reviews and seeks to highlight health inequalities between studies.[15] This has more recently been adapted into the PROGRESS-Plus framework to create a more comprehensive review guideline for identifying health inequalities and characterising populations.[122] Its categories comprise the following: Place of residence, Race, Occupation, Gender, Religion, Education, Social capital, Socio-economic status, Age, Disability, Sexual orientation and other vulnerable and socially excluded groups.

Quality Assessment

Quality assessment of these studies ensures that the findings extracted are reliable and that bias is minimised.[17] Methodology of included literature will be assessed using the NICE Quality Appraisal Checklist for Qualitative Studies,[18] which is based on the Critical Appraisal Skills Programme (CASP) framework, a series of 10 categories designed to make an informed assessment of the design and limitations of qualitative methods.[19] The CASP model has been widely used in similar thematic synthesis reviews to inform the limitations of qualitative methodologies and to comment on the credibility and relevance of included studies.[122] Studies and reports of lower quality will be given less weight in the thematic synthesis and translation stage of the review however they will not be excluded from analysis. Assessment will be checked by two authors independently and then discussed to reach a consensus about the quality of each report.

Researcher's reflexivity

At all stages of the review, the authors will be expected to reflect on their own background and position and how it will affect the design, analysis and interpretation of the research conducted. This will be discussed and described in a 'reflexivity' section during the full text of the review.

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APPENDIX 3: SEARCH STRATEGY FOR SYSTEMATIC REVIEW ON FACTORS AFFECTING ENGAGEMENT IN REMOTE CARE (CHAPTER 2)

Search History:
2. EMBASE; exp HEART VENTRICLE FUNCTION/; 13980 results.
3. EMBASE; exp HEART FAILURE/; 362955 results.
4. EMBASE; exp HEART EDEMA/; 1172 results.
5. EMBASE; "ventricular failure".ti,ab; 5337 results.
6. EMBASE; "heart failure".ti,ab; 190242 results.
7. EMBASE; "cardiac failure".ti,ab; 13534 results.
8. EMBASE; "ventricular dysfunction".ti,ab; 19906 results.
9. EMBASE; "cardiac insufficiency".ti,ab; 4030 results.
10. EMBASE; 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9; 412202 results.
11. EMBASE; exp REMOTE SENSING TECHNOLOGY/ OR exp REMOTE CONSULTATION/; 12059 results.
12. EMBASE; ALGORITHMS/ OR exp ARTIFICIAL INTELLIGENCE/ OR AUTOMATIC DATA PROCESSING/ OR CLOUD COMPUTING/ OR exp COMPUTER GRAPHICS/ OR COMPUTER SIMULATION/ OR exp COMPUTER SYSTEMS/ OR exp COMPUTER COMMUNICATION NETWORKS/ OR exp SOFTWARE/ OR exp MOBILE APPLICATIONS/ OR VIDEO GAMES/ OR WEB BROWSER/ OR exp WORD PROCESSING/ OR exp DATA DISPLAY/; 1286363 results.
13. EMBASE; exp PATTERN RECOGNITION, AUTOMATED/ OR exp "NEURAL NETWORKS (COMPUTER)"/ OR exp TELEMEDICINE/ OR exp TELECOMMUNICATIONS/ OR exp TELEVISION/; 97246 results.
14. EMBASE; ("mhealth" OR "telehealth" OR "telemedicine").ti,ab; 11460 results.
15. EMBASE; exp COMPUTER INTERFACE/; 24644 results.
16. EMBASE; exp TEXT MESSAGING/; 2037 results.
17. EMBASE; ((remote OR home OR tele* OR mobile OR internet OR web OR app OR computer OR "smart phone" OR mhealth OR wireless OR "cell phone" OR software OR hardware) adj3 (care OR management OR monitor* OR health OR administration OR consultation OR communication OR medicine OR technolog* OR support OR sens*)).ti,ab; 93082 results.
18. EMBASE; 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17; 1383914 results.
19. EMBASE; exp HEALTH BEHAVIOR/ OR exp PATIENT COMPLIANCE/ OR exp MEDICATION ADHERENCE/ OR exp TREATMENT REFUSAL/ OR exp ILLNESS BEHAVIOR/ OR exp INFORMATION SEEKING BEHAVIOR/ OR "INHIBITION (PSYCHOLOGY)"/ OR exp PROACTIVE INHIBITION/ OR exp PERSONAL SATISFACTION/ OR exp HELP-SEEKING BEHAVIOR/ OR exp SELF-CONTROL/ OR exp MOTIVATION/ OR DRIVE/ OR GOALS/ OR INTENTION/ OR PERSONALITY/ OR CHARACTER/ OR INDIVIDUALITY/ OR MOTIVATION/ OR exp LIFE STYLE/ OR exp "BEHAVIORAL DISCIPLINES AND ACTIVITIES"/ OR exp BEHAVIOR CONTROL/; 1124888 results.
20. EMBASE; exp INTERDISCIPLINARY COMMUNICATION/ OR exp PHYSICIAN-NURSE RELATIONS/ OR exp NEGOTIATING/ OR exp PROFESSIONAL-PATIENT RELATIONS/ OR exp NURSE-PATIENT RELATIONS/ OR exp PHYSICIAN-PATIENT RELATIONS/ OR TRUST/ OR MORALE/; 1039099 results.
21. EMBASE; exp "ATTITUDE OF HEALTH PERSONNEL"/ OR exp ATTITUDE TO HEALTH/ OR exp HEALTH KNOWLEDGE, ATTITUDES, PRACTICE/ OR exp "PATIENT ACCEPTANCE OF HEALTH CARE"/ OR exp CULTURALLY COMPETENT CARE/; 501449 results.

22. EMBASE; exp PATIENT PARTICIPATION/ OR exp PATIENT SATISFACTION/ OR exp DECISION MAKING/ OR exp HEALTH KNOWLEDGE, ATTITUDES, PRACTICE/ OR exp HEALTH LITERACY/; 445452 results.
23. EMBASE; "adherence".ti,ab; 112446 results.
24. EMBASE; ((physician OR doctor OR nurse OR "healthcare staff" OR "health care staff" OR patient) adj3 (engagement OR acceptability OR compliance OR concordance OR retention OR enthusiasm OR involvement OR refusal OR negotiation OR participation OR satisfaction OR behaviour OR behavior OR motivation OR intention OR "self-control" OR goal OR goals OR morale OR trust OR attitude OR attitudes OR drive OR personality OR character OR individuality OR "life style")).ti,ab; 84951 results.
25. EMBASE; 19 OR 20 OR 21 OR 22 OR 23 OR 24; 2112225 results.
26. EMBASE; 10 AND 18; 16662 results.
27. EMBASE; 25 AND 26; 2540 results.

APPENDIX 4: FIRST ORDER CODES IDENTIFIED IN STUDIES INCLUDED IN SYSTEMATIC REVIEW, WITH ASSOCIATED DESCRIPTIONS (CHAPTER 2)

PATIENT POSITIVE EXPERIENCES	
Psychosocial support	The intervention encourages or promotes interaction with a support group such as friends, family or carers to provide social support for the patient and this can help with feelings of loneliness or isolation or mental health issues.
Patient-to-patient communication	Communication between patients in the same intervention allows peer support, advice and a feeling of togetherness within the group.
Patient-to-staff communication	Remote care strengthens connection between patient and staff and causes a desire for greater communication between two parties
"Feels looked after"	The feeling of being monitored or watched by health-care practitioners which makes patients feel reassured, at ease, and looked after, even when at home.
Clinical knowledge	The intervention provides increased knowledge and information about disease and health status, which is seen as helpful by patients.
Follow up/ co-ordination of care	The intervention allows continuity of care by means of sharing patient information across health disciplines and thus aids the co-ordination of care given to the patient.
Confidence/ motivation in self-care	Exposure to intervention builds patient confidence and motivation in making their own health-related decisions.
Involvement in self-care	Patients having an active role in intervention brings greater independence and sense of control over health.
Confidence in management decisions	Patients feel more confident in the assessment and management of clinicians while using the intervention as they feel it provides staff with more information to make better decisions.
Improvement from usual care	Patient feels the intervention is an improvement from usual care in terms of their recovery, symptoms and quality of life.
User friendly	Intervention is perceived as easy to use by patients.
New technology	Patients take an interest in new health technology and are keen to engage in a novel method of self-care.
Popular	Intervention is used by many patients.
Saves travel time	Remote monitoring saves patients from visits to the clinic, which is a benefit if they suffer from reduced mobility.
Flexible	The intervention has flexible elements which can fit around the patient's lifestyle and allows greater freedom with management of their disease.
Comfort/ Freedom at home	Patients feel more relaxed in their home environment and free to pursue other activities.
PATIENT NEGATIVE EXPERIENCES	
Reliance on staff	Patient sees staff as primary responsible person for their health management and the technology is a tool to help them. They do not experience increased independence as a result.
Lack of patient-to-patient communication	Lack of contact with other patients or support in the group leads to feelings of isolation.
Lack of patient-to-staff communication	Lack of options for patient dialogue with healthcare staff.

Responsibility = anxiety	Even with intervention, patients do not feel comfortable taking responsibility for their own health management, and having to do more for themselves causes anxiety.
Lack of feedback	Lack of feedback from the intervention via the equipment or the clinicians/staff guiding the intervention as to the patient's actions and performance with self-care. Lack of ability to measure improvement.
Unpredictable clinical management	Intervention or actions triggered by it may be perceived as random by the patient and thus reduces their sense of control.
No effect on self-care	Patients feel that the intervention, or actions triggered by the intervention made no difference to their outcome or quality of life, and therefore were not motivated to change self-care behaviour.
Lack of improvement	As a result of intervention, no or little improvement in clinical care or symptoms was perceived, due to lack of the intervention's effect.
Technical difficulties	Intervention malfunctions while in use, and does not reliably work as intended.
Medical jargon	Understanding of the intervention, information, or training phases was disrupted by the presence of medical jargon, which reduces the patient understanding.
Not user friendly	Intervention is not intuitive or easily usable by the patient, or is too complex to apply.
Lack of portability	The device is not portable and causes issues with patients travelling or on holiday.
Technology overwhelming	Patients are not computer literate or technically proficient enough to use the intervention.
Lack of training	Lack of training or provided instructions in the use of the device or software, leaving users confused with its application and use.
Lack of education	Lack of education on the disease process, what to expect, and reason behind using a new intervention, leading to a reduced view of its importance, and misconceptions about their disease state.
Irrelevant training	Patients are given training or education on topics which are not relevant to them or are not flexible enough to encompass their situation.
Unreliable information	Information gained due to intervention is unreliable or untrustworthy.
Intrusive	Comments that the intervention is bulky, or intrusive in the patient's environment.
Cost	The intervention is expensive for the patient.
Lack of privacy/ security	Concerns with patient confidentiality and privacy when using remote care.
Lack of options	Lack of flexibility, information, or treatment options provided by the intervention, which could have been added to make it more effective.
Adds extra concern for carers	The intervention may cause anxiety and insecurity for carers. This may be due to added responsibility, complexity, or the stress of an extra task in their care.
Lack of support for care	Lack of home care and support for utilising the intervention at home and looking after themselves, causing concern for how they will cope, and overburdening current carers.
Extra work = tiring	The intervention adds extra work to the patient's daily life which can be stressful and time consuming.
Uncomfortable at home	Some patients feel that their home environment is uncomfortable during times of illness due to inconveniences such as lack of care, stairs and pain.
Lack of efficiency/ co-ordination	Intervention administrators are not co-ordinated enough resulting in inefficient or mistimed service which is an inconvenience.
Cannot replace hospital care	The intervention cannot replace the environment of a hospital setting; it is not thorough enough, nor provides the same amount of assurances as constant surveillance, and patients would not feel comfortable using the intervention as an alternative.
Extra work for clinicians	Patients are concerned that doctors may be overburdened by extra work brought on by the intervention.

Threat to independence/ control	Intervention threatens the sense of independence and control patients have over their lives and daily routine, and makes them feel restricted and tied to a machine.
Technology not needed	Current care is already optimal and extra technology is not needed to meet the patient's current health needs.
Language barriers	The patient finds it difficult to use the intervention due to a language barrier.

CARER POSITIVE EXPERIENCES

Feel patient is 'looked after'	The perception that the intervention allows the patient to be monitored by healthcare staff more easily and provides a safety net for further problems, which can be reassuring.
Extra support	The intervention supports the carer's efforts in caring for the patient in terms of physical, mental or psychological help where it is needed.
Informative/ educational	The intervention provides information to help the carer in their daily tasks by making them aware of the symptoms and signs of disease for example to help support their patient.
User friendly	The intervention is easy to use and apply by the carer

CARER NEGATIVE EXPERIENCES

Extra responsibility	The intervention adds extra responsibility to the job of caring for the patient by creating an extra task, which may cause stress if not confident with the intervention.
Change is stressful	Carers have a daily routine. The intervention disrupts the daily activities of the carer and forces them to make changes in ways they may not be prepared for. This change adds extra stress to the job of caring.
Causes concern for patient	The intervention adds extra concern and anxiety for the carer by creating an extra task, escalating their fear, and propagating the perception that the disease is progressing and needs constant attention to prevent worsening.
Control taken away	Carers may feel that the intervention takes away some of the control they are used to over the patient's lives and makes them more reliant on healthcare staff.
Invasion of privacy	Intervention may be seen as intrusive, e.g. constant monitoring can threaten the privacy shared between patient and carer.
Lack of education	A lack of information about disease management may leave the carer unsure how to react to different situations of care.
Lack of improvement	Carers may perceive no improvement in symptoms or clinical status from the intervention for the patient
Technical difficulties = stressful	Difficulties caused by malfunction of the intervention can be stressful for carers who rely on it.
Not user friendly	The carer finds the intervention difficult to apply or use
Technology not the solution	Intervention cannot solve the patient's critical needs and cannot replace the services of usual care such as trained carers; or the patient is too ill to make use of the intervention.

HEALTHCARE STAFF POSITIVE EXPERIENCES

Familiarity/ communication with patient	Better familiarity with patient norms and tendencies allows relative comparisons and better personalised decision making. Intervention allows the staff to get to know the patient better and so makes management decisions easier. Emphasis on communication and continuity of care.
Encourages teamwork	The intervention fosters collaboration between healthcare staff and promotes teamwork and communication for better patient care such as by sharing information easily between professionals.

Better knowledge of patient status	Technology allows staff to check in on patients more frequently than regular clinic visits, and gives them a better idea of a patient's condition. This may lead to better decisions. Emphasis on clinical decision making and optimal monitoring.
Pro-active management	Technology helps staff predict negative health outcomes and take actions to prevent them sooner.
Confidence in management	Remote care that increases frequency of monitoring allows medication to be trialled with a shorter review period, and so increases confidence in decisions of management such as medication changes.
Identifies priorities in care	The intervention helps physicians organise information and identifies or presents gaps in care, such as vulnerable patients, or reduced performance, in order to improve quality of care.
Improvement from usual care	The intervention is an improvement in the quality of care from usual practice as viewed from a staff perspective.
Reduces error	The design of the intervention allows extra care in the management of a patient, reducing the risk of errors in care.
Important	A perceived importance of the intervention and the sentiment that the intervention is vital to optimal care of the patient's condition, and is therefore a worthwhile investment.
Encourages patient self-care	Staff's perception that the use of the intervention encourages or motivates patients to care for themselves better, or educates them in improving and getting used to their own self-care.
Increases patient knowledge	The intervention helps patient by increasing knowledge and providing information about management of their disease state and other useful information to make the patient self-reliant.
Staff education	The intervention provides up-to-date information and learning resources for staff and physicians to improve their knowledge and care.
User friendly	Easy for clinicians to use.
Technical support	Non-clinical support is provided in order to aid integration of the system into current practice.
Security/ private	The intervention information is secure, accessible only to staff members it is assigned to, and can be private enough to maintain patient confidentiality.
Automated saves time	Automated process can take the workload away from the staff or clinician and allow easier and quicker patient management than usual care.
No change in workload	Despite the added intervention, the workload of staff is not increased or is even reduced, allowing more time to prioritise to other patients i.e. the intervention is not disruptive to current work patterns.
Incentivisation	The cost of the intervention is offset by incentives which add to the appeal of adopting the intervention such as monetary funding for its use.
Saves travel time	The intervention does or could potentially save the patient travel time.
Local champions	Recognised local champions for the intervention are appointed to aid and support telehealth.
Cost savings	The effect of the intervention is seen to be able to save costs in the long run e.g. by reducing the amount of admissions or critical cases that require further treatment.
Flexible to practice	The intervention can be shaped around the healthcare staff's current practice or adapt to suit different needs as required.

HEALTHCARE STAFF NEGATIVE EXPERIENCES

Perceived dependence on staff	Greater communication and input allowed by remote care makes staff perceive an increased dependence of patients on their support in their daily lives.
Increases patient concern/ confusion	The increased overload of health information and input from the intervention may cause extra concern, worry or confusion for patients who cannot clearly understand.

Lack of patient-to-staff communication	Lack of communication links and options for communication between patients and physicians.
Lack of staff-to-staff communication	New interventions work on a separate system and do not allow communication and referral of patient details to other practitioners and staff, and thus limits inter-professional communication.
Not linked to records	A discord between the new intervention and already established health record systems makes it difficult for staff to adjust to a new system and complicates application.
Inflexible guidance	Staff perceive the intervention as directive and controlling of their patients e.g. giving instructions without adaptation or feedback.
Not user friendly	Difficult, unintuitive, or overly complex for clinicians to use and adapt for clinical work.
Technical difficulties	Problems with the use of technology, or malfunction of any software or hardware used by healthcare professionals.
Computer literacy	Poor computer literacy or technical skills of the staff is a barrier to using the intervention.
Lack of equipment/ support	A lack of equipment such as computer facilities or technical support prevents the intervention from being adopted widely.
Lack of training	Lack of training to use the device or intervention, leading to reduced confidence and knowledge of its application.
Lack of education	Lack of patient's education on disease process, or training for use of the intervention.
No change in patient self-care	Staff perception that the intervention may lead to lack of motivation in self-care for patients.
No improvement	No perceived improvement in the patient's symptoms or clinical health status including mortality or admission rates as a result of the intervention (from the healthcare staff's perspective).
Increased workload	Staff felt that the intervention added to their burden of work by increasing the amount of time required to spend with each patient in the application of the technology, without an increase in compensation.
Slow to change practice	Any statements relating to resistance or reluctance to change current established practice.
Increases errors	The intervention adds an extra layer to the management of a patient's illness, increasing the likelihood of an error in care.
Lack of options	Lack of information, flexibility, treatments and functionality options which could have been added to the intervention to make it more effective.
Patient selection decisions	Intervention is not suitable for all patients and requires a decision for selection on behalf of staff. Not all patients would benefit from being selected.
Cost	Cost and expense considerations from integrating technology from a healthcare staff perspective.
Health inequality	The disparity between the intervention group and the rest of the population who are not able to receive the intervention may create a health inequality gap.
Medicolegal concerns	Statements which involve moral or legal concerns, such as legal issues whether clinicians are obligated to respond to warning alerts immediately.
Information privacy/ security	Concerns and comments relating to the storage and transfer of confidential patient information.
Limits clinical care	The quality of clinical care is not as good with the intervention as with usual care or face-to-face care; More information is felt to be gathered when talking to a patient face-to-face.
Lack of confidence in equipment/ readings	Intervention gives information that may be seen as unreliable, reducing clinician trust in the intervention.
Clinician anxiety	Intervention increases clinician anxiety due to handing over some of their responsibilities to others or to the device.
Lack of evidence of effectiveness	Staff views that there is insufficient evidence to show whether the intervention is effective.

APPENDIX 5: PROGRESS CHART SHOWING THE EXTENT OF DEMOGRAPHIC AND INEQUALITIES DATA REPORTED FROM EACH INCLUDED STUDY (CHAPTER 2)

	N	Residence	Ethnicity	Occupation	Sex	Religion	Education	Social capital	Socio-economic status	Mean age	Disability	Sexual orientation	Vulnerable groups
Abidi 2013	10	-	-	-	-	-	-	-	-	-	-	-	-
Agrell 2000	15	-	-	-	M:7, F:8	-	-	-	-	75	3 (21%)	-	-
Barron 2013	23	-	White: 18 (78%)	Paid work: 8 (35%)	M: 10 (43%) F: 13 (57%)	-	~15 years education	Lives with carer: 19 (83%)	-	Pts: 76.4 Carers: 58.3	-	-	-
Bartlett 2014	7	-	-	-	-	-	-	-	-	-	-	-	-
Bekelman 2014	17	Home	White: 10 (59%)	-	M: 17 (100%)	-	High school: 2 (12%) College: 11 (65%) Postgrad: 3 (18%)	Married: 8 (47%) Separated: 6 (35%) Other: 3 (18%)	-	63	Diabetes: 6 HTN: 12 COPD: 4 OSA: 5 Depress: 3 Alc abuse: 4 Drug abuse: 3	-	-
Dinesen 2008	8	-	-	-	M: 6 (75%) F: 2 (15%)	-	-	6 had spouses 2 lived alone	-	72	-	-	-
Dubois 2001	174	-	-	-	M: 103 (60%) F: 71 (40%)	-	-	-	-	-	-	-	-
Earnest 2004	115	-	White: 90%	8 physician 107 patients (unspecified)	M: 82 (77%)	-	College: 49%	-	Income >$45k: 53%	56	-	-	-

	N	Residence	Ethnicity	Occupation	Sex	Religion	Education	Social capital	Socio-economic status	Mean age	Disability	Sexual orientation	Vulnerable groups
					F: 25 (23%)								
Fairbrother 2014	18	-	-	-	M: 11 (61%) F: 7 (39%)	-	-	-	IMD 0-20: 3 IMD 21-100: 15	<64: 3 65-74: 4 75+: 11	-	-	-
Finkelstein 2011	10	-	-	-	M: 4 (40%) F: 6 (60%)	-	-	-	-	43	-	-	-
Green 2006	30	-	-	Primary care physicians	-	-	-	-	-	-	-	-	-
Gund 2008	2	home	-	retired	-	-	7 year education	Have spouse and children/ grandchildren	-	69 and 79	-	-	-
Hall 2014	15	-	White: 9 (60%) Black: 4 (26.7%) Hispanic: 2 (13.3%)	-	M: 10 (66%) F: 5 (33%)	-	No school: 3 (20%) GED: 1 (6.7%) High school: 2 (13.3%) College: 5 (33.3%) Associate's: 1 (6.7%) Bachelor's: 2 (13.3%) Graduate: 1 (6.7%)	-	-	64	HTN: 11 (73.3%) Diabetes: 3 (20%) COPD: 1 (6.7%) CAD: 4 (26.7%)	-	-
Heisler 2007	20	-	White: 74%	-	M: 44% F: 56%	-	<high school: 13%	Married: 48% Other: 52%	<$15k: 17%	66.3	No hospitalisations in 12 months	-	-

	N	Residence	Ethnicity	Occupation	Sex	Religion	Education	Social capital	Socio-economic status	Mean age	Disability	Sexual orientation	Vulnerable groups
			Black: 22% Other: 4%				High school: 35% Post-high school: 52%	Lives alone: 26% Lives with 1 other: 52% Lives with >1 other: 22%	$15-30k: 27% $30k+: 43%		0: 52% 1: 17% 2-5: 4% 6-10: 26%		
Hunting 2015	39	Home	-	-	M: 20 F: 19	-	-	-	-	73	-	-	-
Johnston 2010	28	-	-	-	-	-	-	-	-	-	-	-	-
Kenealy 2015	171	Home: 118 (69%) Rent: 47 (27%) Retirement home: 6 (4%)	NZ European: 114 (67%) Maori: 32 (19%) Pacific: 25 (15%)	-	M: 105 (61%) F: 66 (39%)	-	Primary school: 28 (16%)	-	<$20k: 78 (46%)	67.1	Vision: 22 Hearing: 10 Diabetes: 60 COPD: 64 HF: 39	-	-
Leslie 2006	30	-	-	-	-	-	-	-	-	-	-	-	-
Lind 2014	14	Home	-	-	M: 11 F: 3	-	-	-	-	84	HF: 14	-	-
Lowrie 2014	65	-	-	-	M: 63% F: 37%	-	-	-	Most deprived area: 40%	-	-	-	-
Lundgren 2015	7	-	-	-	M: 3 F: 4	-	-	-	-	62	IHD: 3 HTN: 3 Arrhythmia: 3 Diabetes: 2 COPD: 1 TIA: 1 Renal disease 1 Psychiatric: 1	-	-
Lynga 2013	23	-	-	-	M:15 F: 5	-	<9 years: 7	Living alone: 5	-	74	-	-	-

	N	Residence	Ethnicity	Occupation	Sex	Religion	Education	Social capital	Socio-economic status	Mean age	Disability	Sexual orientation	Vulnerable groups
							>9 years: 13	Co-habiting: 15					
Nanevicz 2000	50	-	White: 40% African-American: 26% Hispanic: 12 Asian: 4% Pacific: 14% Other: 4%	Unemployed: 64% Employed: 12% Retired: 24%	M: 40 F: 10	-	High school or less: 56% College: 38% Postgrad: 6%	Single: 50% Married: 38% Divorced 4% Partner 8%	-	60	HTN: 54% Diabetes: 26%	-	-
Nasstrom 2015	19	Home care units	-	-	M: 13 F: 6	-	Elementary school: 10 Primary school: 2 High school: 7	-	-	77	-	-	-
Odeh 2014	7	-	-	Nurses	-	-	Nursing level education	-	-	-	-	-	-
Paget 2010	22	Home	-	-	-	-	-	-	-	-	-	-	-
Payne 2015	7	-	White: 5 African-American: 1 Chinese: 1	Employed: 1	M: 5 F: 2	-	Post-secondary education: 6	Married: 5	-	57	Disability: 1	-	-
Rahimpor 2008	77	-	Included Anglo/ Celtic, Italian, Chinese, Assyrian,	-	-	-	-	-	-	71	-	-	-

	N	Residence	Ethnicity	Occupation	Sex	Religion	Education	Social capital	Socio-economic status	Mean age	Disability	Sexual orientation	Vulnerable groups
			Russian, Greek and Pacific										
Riley 2013	15	-	White: 14 (93%) South Asian: 1 (7%)	Retired: 14 (93%) Employment: 1 (7%)	M: 11 (73%) F: 4 (27%)	-	-	Lived alone: 8 (53%)	-	74	-	-	-
Sanders 2012	16	-	-	-	M: 18 F: 8	-	-	-	-	71	-	-	-
Selman 2015	15	-	Caucasian: 14 Other: 1	-	M: 3 F: 9	-	Some college: 4 College degree: 2 Graduate degree: 5	Live alone: 4 Assisted living: 2 With spouse: 3 With son: 1 With family friend: 1	-	71.2	-	-	-
Seto 2010	94	-	Caucasian: 71 African Canadian: 7 Southeast Asian: 4 Chinese: 4 Other: 7	Full time: 27 Part time: 4 Disabled: 37 Retired: 15 Unemployed 11	M: 74 F: 20	-	< high school: 7 High school: 25 Trade: 16 College: 37 Post-grad: 8	Married: 62 Never married: 17 Divorced: 10 Widowed: 4	<$15k: 20 $15-30: 17 $30-50: 17 $50-75: 14 >$75k: 14	54.6	Disabled: 37	-	-
Seto 2012	22	-	-	-	M: 18 F: 4	-	-	-	-	57	-	-	-
Sharma 2010	16	-	-	Nurses, support workers	M: 2 F: 16	-	-	-	-	-	-	-	-

	N	Residence	Ethnicity	Occupation	Sex	Religion	Education	Social capital	Socio-economic status	Mean age	Disability	Sexual orientation	Vulnerable groups
Sharma 2014	20	-	-	Clinicians	-	-	-	-	-	-	-	-	-
Stromberg 2002	42	-	-	-	M: 24 F: 18	-	12+ years education: 29%	-	-	74	-	-	-
Svagard 2014	9	-	-	-	F: 9	-	-	-	-	-	-	-	-
Taylor 2015	105	-	-		-	-	-	-	-	-	-	-	-
Whitten 1998	4	-	-	Nurses	F: 4	-	Education to nursing level	-	-	-	-	-	-
Whitten 2009	50	-	White: 80% Black: 20%	-	M: 34% F: 66%	-	-	Lives alone: 56% With spouse: 44%	Public health service: 47	78	Obesity: 30%	-	-
Woodend 2008	249	-	-	-	M: 74% F: 26%	-	-	-	-	66	-	-	-
Young 2008	5	-	Jewish: 3 Ethiopian: 1 Other: 1	Retired	M: 3 F: 2	Jewish: 3	-	Married: 1 Widowed: 3 Unmarried: 1	-	85	-	-	-
Zulman 2015	53	-	White: 43 (81%) Black: 3 (6%) Hispanic: 5 (9%) Other: 7 (13%)	Unemployed: 23 (44%) Retired: 25 (48%) Employed: 17 (33%)	M: 39 (74%) F: 14 (26%)	-	High school: 4 (8%) College: 23 (44%) Degree: 25 (48%)	-	<$50k: 22 (43%) $50-75: 8 (16%) >$75k: 21 (41%)	59	Disabled or unemployed: 23 (44%)	-	-

APPENDIX 6: NICE QUALITY APPRAISAL CHECKLIST FOR QUALITATIVE STUDIES (CHAPTER 2)

	Theoretical approach		*Methodology*		*Trustworthiness*			*Analysis*						*Ethics*	Overall rating
	Qualitative approach	Study purpose	Study design	Data collection	Role of researcher	Context	Reliable methods	Rigorous data analysis	Rich data	Reliable analysis	Convincing findings	Relevant findings	Conclusions	Clear and coherent reporting	
Abidi 2013	Appropriate	Clear	Defensible	Appropriate	NR	Clear	Not sure	Rigorous	Poor	Reliable	Not convincing	Irrelevant	Adequate	Appropriate	+
Agrell 2000	Appropriate	Clear	Defensible	Appropriate	NR	Unclear	Unreliable	Not rigorous	Poor	Unreliable	Not convincing	Relevant	Adequate	Inappropriate	+
Barron 2013	Appropriate	Clear	Indefensible	Inappropriate	NR	Clear	Reliable	Not rigorous	Poor	Unreliable	Not convincing	Relevant	Inadequate	Inappropriate	-
Bartlett 2014	Appropriate	Clear	Defensible	Appropriate	NR	Not sure	Unreliable	Rigorous	Rich	Reliable	Convincing	Relevant	Adequate	Appropriate	+
Bekelman 2014	Appropriate	Clear	Defensible	Appropriate	Unclear	Unclear	Not sure	Rigorous	Poor	Not sure	Not sure	Relevant	Adequate	Inappropriate	+
Dinesen 2008	Appropriate	Clear	Defensible	Appropriate	Unclear	Clear	Reliable	Rigorous	Poor	Reliable	Convincing	Relevant	Adequate	Appropriate	++
Dubois 2001	Appropriate	Clear	Defensible	Appropriate	Clear	Clear	Reliable	Not rigorous	Poor	Unreliable	Convincing	Relevant	Adequate	Appropriate	+
Earnest 2004	Appropriate	Clear	Defensible	Appropriate	NR	Not sure	Reliable	Rigorous	Poor	Reliable	Convincing	Relevant	Adequate	Appropriate	++
Fairbrother 2014	Appropriate	Clear	Defensible	Appropriate	Clear	Clear	Reliable	Rigorous	Rich	Reliable	Convincing	Relevant	Adequate	Appropriate	++
Finkelstein 2011	Appropriate	Clear	Defensible	Not sure	NR	Unclear	Not sure	Not rigorous	Poor	Unreliable	Not sure	Irrelevant	Inadequate	Inappropriate	-
Green 2006	Appropriate	Clear	Defensible	Appropriate	NR	Not sure	Not sure	Rigorous	Rich	Not sure	Convincing	Relevant	Adequate	Inappropriate	+
Gund 2008	Appropriate	Clear	Indefensible	Appropriate	NR	Unclear	Unreliable	Not rigorous	Poor	Reliable	Convincing	Relevant	Adequate	Inappropriate	-
Hall 2014	Appropriate	Clear	Defensible	Appropriate	NR	Not sure	Reliable	Rigorous	Rich	Reliable	Convincing	Relevant	Adequate	Not sure	+
Heisler 2007	Not sure	Clear	Defensible	Appropriate	Unclear	Unclear	Not sure	Not rigorous	Poor	Reliable	Convincing	Relevant	Not sure	Not sure	+
Hunting 2015	Appropriate	Clear	Defensible	Appropriate	Clear	Clear	Reliable	Rigorous	Rich	Reliable	Convincing	Relevant	Adequate	Appropriate	++
Johnston 2010	Appropriate	Unclear	Defensible	Not sure	NR	Unclear	Unreliable	Not rigorous	Poor	Unreliable	Not sure	Irrelevant	Inadequate	Inappropriate	-

	Theoretical approach		*Methodology*		*Trustworthiness*			*Analysis*						*Ethics*	Overall rating
	Qualitative approach	Study purpose	Study design	Data collection	Role of researcher	Context	Reliable methods	Rigorous data analysis	Rich data	Reliable analysis	Convincing findings	Relevant findings	Conclusions	Clear and coherent reporting	
Kenealy 2015	Appropriate	Clear	Defensible	Appropriate	NR	Clear	Not sure	Rigorous	Rich	Reliable	Convincing	Relevant	Adequate	Appropriate	++
Leslie 2006	Appropriate	Clear	Not sure	Not sure	NR	Not sure	Not sure	Not rigorous	Poor	Not sure	Not convincing	Relevant	Not sure	Not sure	-
Lind 2014	Appropriate	Clear	Defensible	Appropriate	NR	Unclear	Unreliable	Not rigorous	Poor	Unreliable	Convincing	Relevant	Not sure	Appropriate	+
Lowrie 2014	Appropriate	Clear	Defensible	Appropriate	NR	Not sure	Not sure	Not rigorous	Rich	Not sure	Convincing	Partially relevant	Adequate	Not sure	+
Lundgren 2015	Appropriate	Clear	Indefensible	Appropriate	NR	Not sure	Not sure	Not rigorous	Poor	Reliable	Not convincing	Relevant	Not sure	Appropriate	+
Lynga 2013	Appropriate	Clear	Defensible	Appropriate	NR	Not sure	Reliable	Rigorous	Rich	Reliable	Convincing	Relevant	Adequate	Appropriate	++
Nanevicz 2000	Not sure	Clear	Defensible	Appropriate	NR	Clear	Unreliable	Rigorous	Not sure	Not sure	Not sure	Relevant	Adequate	Appropriate	-
Nasstrom 2015	Appropriate	Clear	Defensible	Appropriate	Unclear	Clear	Not sure	Rigorous	Rich	Reliable	Convincing	Relevant	Adequate	Appropriate	+
Odeh 2014	Appropriate	Clear	Not sure	Not sure	NR	Unclear	Not sure	Rigorous	Rich	Unreliable	Convincing	Relevant	Adequate	Not sure	+
Paget 2010	Appropriate	Clear	Indefensible	Inappropriate	NR	Unclear	Unreliable	Not rigorous	Poor	Unreliable	Not convincing	Relevant	Not sure	Inappropriate	-
Payne 2015	Appropriate	Clear	Defensible	Appropriate	Clear	Clear	Not sure	Not rigorous	Not sure	Reliable	Not sure	Relevant	Adequate	Appropriate	+
Rahimpour 2008	Appropriate	Clear	Defensible	Appropriate	Clear	Not sure	Reliable	Rigorous	Not sure	Reliable	Convincing	Relevant	Adequate	Appropriate	++
Riley 2013	Appropriate	Clear	Defensible	Appropriate	NR	Clear	Reliable	Rigorous	Rich	Reliable	Convincing	Relevant	Adequate	Appropriate	++
Sanders 2012	Appropriate	Clear	Defensible	Appropriate	Unclear	Clear	Reliable	Rigorous	Not sure	Reliable	Convincing	Relevant	Adequate	Appropriate	++
Selman 2015	Appropriate	Clear	Defensible	Appropriate	Unclear	Not sure	Unreliable	Not sure	Not sure	Reliable	Convincing	Relevant	Adequate	Appropriate	+
Seto 2010	Appropriate	Clear	Defensible	Appropriate	Unclear	Clear	Reliable	Rigorous	Rich	Reliable	Convincing	Relevant	Adequate	Appropriate	++
Seto 2012	Appropriate	Clear	Defensible	Appropriate	NR	Clear	Reliable	Rigorous	Rich	Reliable	Convincing	Relevant	Adequate	Inappropriate	++
Sharma 2010	Appropriate	Clear	Not sure	Not sure	NR	Clear	Not sure	Rigorous	Rich	Not sure	Convincing	Relevant	Adequate	Not sure	-

	Theoretical approach		*Methodology*		*Trustworthiness*			*Analysis*						*Ethics*	Overall rating
	Qualitative approach	Study purpose	Study design	Data collection	Role of researcher	Context	Reliable methods	Rigorous data analysis	Rich data	Reliable analysis	Convincing findings	Relevant findings	Conclusions	Clear and coherent reporting	
Sharma 2014	Appropriate	Clear	Not sure	Appropriate	Unclear	Not sure	Not sure	Rigorous	Not sure	Not sure	Convincing	Relevant	Adequate	Appropriate	+
Stromberg 2002	Appropriate	Clear	Not sure	Not sure	NR	Clear	Not sure	Not rigorous	Not sure	Not sure	Not sure	Relevant	Adequate	Not sure	-
Svagard 2014	Appropriate	Clear	Not sure	Not sure	Unclear	Unclear	Not sure	Not sure	Poor	Not sure	Not sure	Relevant	Adequate	Inappropriate	-
Taylor 2015	Appropriate	Clear	Defensible	Appropriate	NR	Clear	Reliable	Rigorous	Rich	Reliable	Convincing	Relevant	Adequate	Appropriate	++
Whitten 1998	Appropriate	Clear	Not sure	Not sure	Unclear	Unclear	Not sure	Not sure	Poor	Not sure	Convincing	Relevant	Adequate	Inappropriate	-
Whitten 2009	Not sure	Clear	Indefensible	Not sure	NR	Unclear	Unreliable	Not sure	Poor	Not sure	Not sure	Relevant	Not sure	Not sure	-
Woodend 2008	Not sure	Clear	Not sure	Appropriate	NR	Unclear	Unreliable	Not rigorous	Poor	Unreliable	Not sure	Partially relevant	Not sure	Appropriate	-
Young 2008	Appropriate	Clear	Not sure	Appropriate	Unclear	Clear	Reliable	Rigorous	Poor	Not sure	Convincing	Relevant	Adequate	Appropriate	+
Zulman 2015	Appropriate	Clear	Defensible	Appropriate	NR	Clear	Reliable	Rigorous	Rich	Reliable	Convincing	Relevant	Adequate	Appropriate	++

APPENDIX 7: FIRST ORDER QUALITATIVE CODE FREQUENCIES AND QUALITY OF EACH STUDY WITHIN FIRST ORDER CODES (CHAPTER 2)

Patient positive experiences:

Code	Fq	References		
"Feels looked after"	26	Dinesen 2008 ++ Earnest 2004 ++ Fairbrother 2014 ++ Hunting 2015 ++ Kenealy 2015 ++ Lynga 2013 ++ Payne 2015 ++ Rahimpour 2008 ++ Riley 2012 ++ Seto 2010 ++ Seto 2012 ++	Agrell 2000 + Bartlett 2014 + Bekelman 2014 + Dubois 2001 + Hall 2014 + Lind 2014 + Lowrie 2014 + Nasstrom 2015 + Young 2008 +	Finkelstein 2011 - Gund 2008 - Johnston 2010 - Paget 2010 - Whitten 2009 - Woodend 2008 -
Confidence/ motivation in self-care	25	Dinesen 2008 ++ Earnest 2004 ++ Fairbrother 2014 ++ Hunting 2015 ++ Kenealy 2015 ++ Lynga 2013 ++ Rahimpour 2008 ++ Riley 2012 ++ Seto 2010 ++ Seto 2012 ++ Zulman 2015 ++	Bartlett 2014 + Bekelman 2014 + Hall 2014 + Heisler 2007 + Lowrie 2014 + Lundgren 2015 + Nasstrom 2015 + Selman 2015 +	Finkelstein 2011 - Johnston 2010 - Paget 2010 - Svagard 2014 - Whitten 2009 - Woodend 2008 -
Clinical knowledge	23	Dinesen 2008 ++ Earnest 2004 ++ Fairbrother 2014 ++ Kenealy 2015 ++ Lynga 2013 ++ Payne 2015 ++ Rahimpour 2008 ++ Riley 2012 ++ Seto 2012 ++ Zulman 2015 ++	Bartlett 2014 + Bekelman 2014 + Hall 2014 + Lind 2014 + Lundgren 2015 + Lowrie 2014 + Nasstrom 2015 +	Finkelstein 2011 - Nanevicz 2000 - Paget 2010 - Stromberg 2002 - Whitten 2009 - Woodend 2008 -
Involvement in self-care	17	Dinesen 2008 ++ Earnest 2004 ++ Fairbrother 2014 ++ Kenealy 2015 ++ Lynga 2013 ++ Rahimpour 2008 ++ Riley 2012 ++ Seto 2010 ++ Seto 2012 ++	Bartlett 2014 + Bekelman 2014 + Lind 2014 + Lowrie 2014 + Nasstrom 2015 + Selman 2015 +	Paget 2010 -

Code	Fq	References		
		Zulman 2015 ++		
Patient-to-staff communication	16	Dinesen 2008 ++ Earnest 2004 ++ Fairbrother 2014 ++ Hunting 2015 ++ Kenealy 2015 ++ Lynga 2013 ++ Seto 2012 ++ Riley 2012 ++	Agrell 2000 + Bekelman 2014 + Hall 2014 + Lind 2014 + Lowrie 2014 + Nasstrom 2015 + Young 2008 +	Gund 2008 -
User-Friendly	16	Bartlett 2014 + Fairbrother 2014 ++ Hunting 2015 ++ Lynga 2013 ++ Rahimpour 2008 ++ Riley 2012 ++ Seto 2012 ++	Bekelman 2014 + Lind 2014 + Selman 2015 +	Baron 2013 - Finkelstein 2011 - Gund 2008 - Paget 2010 - Svagard 2014 - Whitten 2009 -
Confidence in management decisions	11	Dinesen 2008 ++ Earnest 2004 ++ Kenealy 2015 ++ Lynga 2013 ++ Rahimpour 2008 ++ Riley 2012 ++	Bartlett 2014 + Dubois 2001 + Lind 2014 + Nasstrom 2015 + Young 2008 +	
Saves travel time	11	Hunting 2015 ++ Kenealy 2015 ++ Rahimpour 2008 ++ Seto 2010 ++ Seto 2012 ++ Zulman 2015 ++	Dubois 2001 + Hall 2014 + Lind 2014 + Lowrie 2014 +	Gund 2008 -
Flexible	10	Dinesen 2008 ++ Kenealy 2015 ++ Riley 2012 ++ Seto 2010 ++ Seto 2012 ++	Dubois 2001 + Lundgren 2015 +	Finkelstein 2011 - Gund 2008 - Stromberg 2002 -
Popular	10	Earnest 2004 ++ Fairbrother 2014 ++ Kenealy 2015 ++ Rahimpour 2008 ++	Lowrie 2014 +	Finkelstein 2011 - Gund 2008 - Nanevicz 2000 - Svagard 2014 - Whitten 2009 -
Improvement from usual care	10	Dinesen 2008 ++ Kenealy 2015 ++ Rahimpour 2008 ++ Seto 2012 ++	Bartlett 2014 + Hall 2014 + Lind 2014 + Lowrie 2014 + Nasstrom 2015 + Young 2008 +	
Comfort/ Freedom at home	9	Dinesen 2008 ++ Riley 2012 ++ Rahimpour 2008 ++	Dubois 2001 + Selman 2015 + Hall 2014 + Young 2008 +	Paget 2010 - Whitten 2009 -
Psychosocial support	8	Kenealy 2015 ++ Payne 2015 ++ Rahimpour 2008 ++	Bekelman 2014 + Dubois 2001 + Heisler 2007 + Lowrie 2014 +	Johnston 2010 -

Code	Fq	References		
New technology	6	Dinesen 2008 ++ Kenealy 2015 ++ Lynga 2013 ++ Riley 2012 ++	Bartlett 2014 + Hall 2014 +	
Follow up/co-ordination of care	4	Earnest 2004 ++ Hunting 2015 ++ Rahimpour 2008 ++	Young 2008 +	
Patient-to-patient communication	3	Dinesen 2008 ++	Heisler 2007 + Nasstrom 2015 +	

Patient negative experiences:

Code	Fq	References		
Technical Difficulties	18	Dinesen 2008 ++ Fairbrother 2014 ++ Kenealy 2015 ++ Rahimpour 2008 ++ Sanders 2012 ++	Bartlett 2014 + Dubois 2001 + Hall 2014 + Lynga 2013 ++ Lundgren 2015 + Selman 2015 +	Gund 2008 - Johnston 2010 - Nanevicz 2000 - Paget 2010 - Svagard 2014 - Whitten 2009 - Woodend 2008 -
Not User Friendly	16	Earnest 2004 ++ Hunting 2015 ++ Payne 2015 ++ Rahimpour 2008 ++ Riley 2012 ++ Sanders 2012 ++ Seto 2010 ++	Agrell 2000 + Bekelman 2014 + Lind 2014 + Selman 2015 +	Baron 2013 - Finkelstein 2011 - Gund 2008 - Johnston 2010 - Svagard 2014 -
Lack of patient-to-staff communication	13	Earnest 2004 ++ Fairbrother 2014 ++ Lynga 2013 ++ Rahimpour 2008 ++ Riley 2012 ++ Sanders 2012 ++ Zulman 2015 ++	Agrell 2000 + Bekelman 2014 + Dubois 2001 + Heisler 2007 + Young 2008 +	Johnston 2010 -
Lack of improvement	11	Fairbrother 2014 ++ Riley 2012 ++ Sanders 2012 ++	Bartlett 2014 + Bekelman 2014 + Dubois 2001 + Heisler 2007 + Lind 2014 + Lowrie 2014 + Young 2008 +	Johnston 2010 -
Technology overwhelming	8	Rahimpour 2008 ++ Sanders 2012 ++ Seto 2010 ++	Bartlett 2014 + Hall 2014 + Lind 2014 +	Stromberg 2002 - Woodend 2008 -
Lack of education	8	Earnest 2004 ++ Zulman 2015 ++	Bekelman 2014 + Hall 2014 + Lowrie 2014 +	Barron 2013 - Johnston 2010 - Stromberg 2002 -
Cost	8	Fairbrother 2014 ++ Rahimpour 2008 ++	Bartlett 2014 + Dubois 2001 + Hall 2014 +	Johnston 2010 - Woodend 2008 -

Code	Fq	References		
		Seto 2012 ++		
Reliance of staff	8	Fairbrother 2014 ++ Hunting 2015 ++ Riley 2012 ++ Sanders 2012 ++ Seto 2012 ++	Bekelman 2014 + Hall 2014 + Nasstrom 2015 +	
No effect on self-care	7	Fairbrother 2014 ++ Hunting 2015 ++ Lynga 2013 ++ Riley 2012 ++	Bartlett 2014 + Heisler 2007 + Selman 2015 +	
Extra work = tiring	7	Kenealy 2015 ++ Sanders 2012 ++	Bartlett 2014 + Dubois 2001 + Hall 2014 + Lundgren 2015 +	Svagard 2014 -
Responsibility = anxiety	7	Fairbrother 2014 ++ Lynga 2013 ++ Rahimpour 2008 ++ Seto 2012 ++ Zulman 2015 ++	Dubois 2001 +	Svagard 2014 -
Lack of training	6	Earnest 2004 ++ Rahimpour 2008 ++ Sanders 2012 ++	Dubois 2001 + Heisler 2007 +	Barron 2013 -
Lack of options	6	Rahimpour 2008 ++	Bartlett 2014 + Bekelman 2014 + Dubois 2001 + Nasstrom 2015 +	Gund 2008 -
Lack of privacy/ security	6	Earnest 2004 ++ Seto 2010 ++ Seto 2012 ++	Agrell 2000 + Dubois 2001 + Hall 2014 +	
Intrusive	5	Fairbrother 2014 ++ Hunting 2015 ++	Bartlett 2014 +	Gund 2008 - Johnston 2010 -
Lack of efficiency/ co-ordination	4	Sanders 2012 ++ Zulman 2015 ++	Dubois 2001 + Lowrie 2014 +	
Lack of feedback	3	Lynga 2013 ++	Bartlett 2014 +	Johnston 2010 -
Unpredictable clinical management	3	Fairbrother 2014 ++ Sanders 2012 ++	Dubois 2001 +	
Cannot replace hospital care	3	Sanders 2012 ++	Dubois 2001 +	Whitten 2009 -
Irrelevant training	3	Hunting 2015 ++	Bartlett 2014 + Bekelman 2014 +	
Lack of portability	3	Hunting 2015 ++ Kenealy 2015 ++	Bartlett 2014 +	
Lack of patient-to-patient communication	2	Zulman 2015 ++	Heisler 2007 +	
Medical Jargon	2	Earnest 2004 ++	Hall 2014 +	
Threat to independence/ control	2	Sanders 2012 ++		Woodend 2008 -
Unreliable information	2	Seto 2010 ++	Hall 2014 +	
Adds extra concern for carers	2	Dinesen 2008 ++	Dubois 2001 +	

Code	Fq	References		
Extra work for clinicians	2	Rahimpour 2008 ++ Seto 2010 ++		
Lack of support for care	2		Dubois 2001 +	Paget 2010 -
Language barriers	2	Hunting 2015 ++ Seto 2012 ++		
Uncomfortable at home	1		Dubois 2001 +	
Technology not needed	1	Sanders 2012 ++		

Carer positive experiences:

Code	Fq	References		
Feels patient is 'looked after'	6	Dinesen 2008 ++ Hunting 2015 ++ Kenealy 2015 ++ Seto 2012 ++	Dubois 2001 +	Johnston 2010 -
Extra support	3	Dinesen 2008 ++		Barron 2013 - Johnston 2010 -
Informative/ educational	2	Kenealy 2015 ++		Barron 2013 -
User friendly	1			Barron 2013 -

Carer negative experiences:

Code	Fq	References		
Change is stressful	3	Dinesen 2008 ++ Sanders 2012 ++	Dubois 2001 +	
Extra responsibility	2	Dinesen 2008 ++	Dubois 2001 +	
Lack of education	2	Dinesen 2008 ++		Barron 2013 -
Causes concern for patient	1	Dinesen 2008 ++		
Control taken away	1	Dinesen 2008 ++		
Invasion of privacy	1	Dinesen 2008 ++		
Lack of improvement	1	Dinesen 2008 ++		
Technical difficulties = stressful	1	Dinesen 2008 ++		
Not user friendly	1			Barron 2013 -
Technology not the solution	1	Sanders 2012 ++		

Healthcare staff positive experiences:

Code	Fq	References		
Encourages patient self-care	10	Earnest 2004 ++ Hunting 2015 ++ Kenealy 2015 ++ Seto 2010 ++ Seto 2012 ++	Lowrie 2014 + Odeh 2014 +	Johnston 2010 - Svagard 2014 - Whitten 1998 -
Familiarity/ Communication with patient	9	Earnest 2004 ++ Fairbrother 2014 ++ Kenealy 2015 ++ Seto 2012 ++	Lowrie 2014 + Odeh 2014 + Sharma 2014 +	Stromberg 2002 - Whitten 1998 -
Increases patient knowledge	8	Earnest 2004 ++ Kenealy 2015 ++	Lowrie 2014 +	Leslie 2006 - Stromberg 2002 -

Code	Fq	References		
		Seto 2012 ++		Svagard 2014 - Whitten 1998 -
Confidence in management	6	Fairbrother 2014 ++ Seto 2012 ++	Green 2006 + Lowrie 2014 +	Johnston 2010 - Leslie 2006 -
Important	6	Earnest 2004 ++ Hunting 2015 ++ Kenealy 2015 +	Lowrie 2014 +	Johnston 2010 - Leslie 2006 -
Better knowledge of patient status	6	Fairbrother 2014 ++ Hunting 2015 ++ Seto 2012 ++	Green 2006 + Lowrie 2014 +	Svagard 2014 -
Automated saves time	5	Hunting 2015 ++ Taylor 2015 ++		Johnston 2010 - Leslie 2006 - Stromberg 2002 -
User friendly	5		Green 2006 + Lowrie 2014 +	Leslie 2006 - Paget 2010 - Svagard 2014 -
Encourages teamwork	4	Hunting 2015 ++ Taylor 2015 ++	Green 2006 + Sharma 2014 +	
Pro-active management	4	Fairbrother 2014 ++ Seto 2010 ++ Seto 2012 ++	Lowrie 2014 +	
Technical support	4	Hunting 2015 ++	Green 2006 + Sharma 2014 +	Leslie 2006 -
Improvement from usual care	4	Hunting 2015 ++ Seto 2012 ++	Sharma 2014 +	Leslie 2006 -
Identifies priorities in care	3		Green 2006 + Sharma 2014 +	Leslie 2006 -
Staff education	3	Taylor 2015 ++	Green 2006 +	Leslie 2006 -
No change in workload	3	Earnest 2004 ++ Kenealy 2015 ++	Green 2006 +	
Saves travel time	3	Hunting 2015 ++ Seto 2010 ++ Seto 2012 ++		
Reduces error	2	Earnest 2004 ++	Green 2006 +	
Local champions	2	Hunting 2015 ++ Taylor 2015 ++		
Security/ Privacy	1		Green 2006 +	
Incentivisation	1		Green 2006 +	
Cost savings	1	Seto 2012 ++		
Flexible to practice	1	Seto 2012 ++		

Healthcare staff negative experiences:

Code	Fq	References		
Increased workload	13	Fairbrother 2014 ++ Hunting 2015 ++ Kenealy 2015 ++ Seto 2010 ++ Seto 2012 ++ Taylor 2015 ++	Lowrie 2014 + Odeh 2014 + Sharma 2014 +	Leslie 2006 - Nanevicz 2000 – Paget 2010 - Sharma 2010 -
Slow to change practice	8	Hunting 2015 ++ Taylor 2015 ++	Odeh 2014 + Sharma 2014 +	Johnston 2010 - Leslie 2006 - Paget 2010 - Sharma 2010 -
Lack of equipment/ support	8	Seto 2012 ++ Taylor 2015 ++	Odeh 2014 + Sharma 2014 +	Leslie 2006 - Paget 2010 - Sharma 2010 - Whitten 1998 -
Not user friendly	7	Seto 2010 ++	Abidi 2013 +	Gund 2008 - Leslie 2006 - Stromberg 2002 - Whitten 1998 -
Lack of training	7	Fairbrother 2014 ++ Taylor 2015 ++	Abidi 2013 + Lowrie 2014 + Odeh 2014 + Sharma 2014 +	Paget 2010 - Sharma 2010 -
Lack of patient-to-staff communication	7	Earnest 2004 ++ Fairbrother 2014 ++ Hunting 2015 ++	Lowrie 2014 + Sharma 2014 +	Stromberg 2002 - Whitten 1998 -
Cost	7	Earnest 2004 ++ Fairbrother 2014 ++ Hunting 2015 ++ Seto 2012 ++ Taylor 2015 ++	Odeh 2014 +	Johnston 2010 -
Patient selection decisions	7	Fairbrother 2014 ++ Hunting 2015 ++ Taylor 2015 ++	Odeh 2014 +	Johnston 2010 – Paget 2010 - Sharma 2010 -
Increases errors	6	Earnest 2004 ++ Kenealy 2015 ++ Seto 2010 ++	Sharma 2014 +	Paget 2010 - Sharma 2010 -
Technical difficulties	6	Kenealy 2015 ++ Taylor 2015 ++	Odeh 2014 +	Paget 2010 - Svagard 2014 - Whitten 1998 -
Lack of staff-to-staff communication	5	Fairbrother 2014 ++ Hunting 2015 ++	Lowrie 2014 + Odeh 2014 + Sharma 2014 +	
Not linked to records	5	Fairbrother 2014 ++ Hunting 2015 ++ Seto 2012 ++	Odeh 2014 + Sharma 2014 +	
Inflexible guidance	4	Fairbrother 2014 ++	Abidi 2013 + Lowrie 2014 +	Leslie 2006 -
Lack of education	4	Fairbrother 2014 ++	Abidi 2013 + Lowrie 2014 +	Leslie 2006 -

Code	Fq	References		
Increases patient concern/ confusion	4	Earnest 2004 ++	Sharma 2014 +	Paget 2010 - Sharma 2010 -
Lack of options	4		Odeh 2014 +	Gund 2008 - Leslie 2006 - Svagard 2014 -
No improvement	3	Earnest 2004 ++ Fairbrother 2014 ++		Johnston 2010 -
Lack of confidence in equipment/ readings	3	Taylor 2015 ++	Sharma 2014 +	Sharma 2010 -
Health inequality	3	Earnest 2004 ++ Hunting 2015 ++	Sharma 2014 +	
Limits clinical care	3		Sharma 2014 +	Sharma 2010 - Whitten 1998 -
No change in patient self-care	2	Fairbrother 2014 ++	Lowrie 2014 +	
Clinician anxiety	2	Taylor 2015 ++		Sharma 2010 -
Lack of evidence of effectiveness	2	Taylor 2015 ++	Odeh 2014 +	
Perceived dependence on staff	2	Fairbrother 2014 ++ Hunting 2015 ++		
Computer literacy	2			Leslie 2006 - Whitten 1998 -
Information privacy/security	1	Seto 2010 ++		
Medicolegal concerns	1	Seto 2010 ++		

APPENDIX 8: SECOND ORDER CODES GENERATED FROM FIRST ORDER CODES (CHAPTER 2)

Patient positive experiences:

Second order codes	First order codes
Improves clinical care	Improvement from normal care
	Better follow up and co-ordination of care
	Patient feels 'looked after'
	Increased confidence in staff's management
Improves self-care	Increased knowledge of their condition
	Increased confidence and motivation for self-care
	Increased involvement in self-care
Improved communication	Psychosocial support
	Patient to patient communication
Accessible Design	User friendly
	Popular with patients
	New technology is novel and exciting
Adds Convenience	Saves travel time
	Increased comfort and freedom at home
	Intervention is flexible to patient's lifestyle

Patient negative experiences:

Second order codes	First order codes
Poor design / Inaccessible to patients	Medical Jargon
	New technology overwhelming
	Intrusive
	Not user friendly
	High Cost
	Technical difficulties
	Lack of portability
	Lack of feedback
	Gives unreliable information
	Lack of privacy and security
Loss of control	Unpredictable changes in management
	Pt feels uncomfortable at home
	Lack of flexibility
	Intervention threatens independence and control
	Reliance on staff
Increased burden of work and responsibility	Extra work is tiring
	Lack of extra support to help cope with intervention
	More responsibility causes anxiety
	Extra concern for carers
	Worries about extra work for staff
Does not contribute to care	No effect on self-care
	Technology not needed
	Cannot replace hospital care

Second order codes	First order codes
	Lack of improvement from normal care
	Lack of co-ordination and efficiency
Poor communication	Lack of patient to patient communication
	Lack of patient to staff communication
	Language barriers
Inadequate patient education	Lack of education on disease and health condition
	Lack of training for intervention
	Irrelevant training for intervention

Carer positive experiences:

Second order codes	First order codes
Improved care	Feels the patient is 'looked after'
	Leads to extra support
Improves Education	Educational and informative
Accessible Design	User friendly

Carer negative experiences:

Second order codes	First order codes
Increases stress of care	Change in routine is stressful
	Extra responsibility
	Adds extra concerns for patient and carer
Technology is not needed	Technology is not enough
	Lack of improvement
Poor education	Lack of education
Inaccessible design	Not user friendly
	Technical difficulties are stressful
Loss of control	Invasion of privacy
	Control is taken away

Healthcare staff positive experiences:

Second order codes	First order codes
Improved communication	Encourages teamwork within staff
	Familiarity and communication with patient
Accessible Design	Maintains privacy and security
	User friendly
	Incentives provided
	Cost savings
	Technical support provided
	Flexible to practice
Saves Time	Automated process saves time
	No change in workload
	Saves travel time for patients
Enhances Quality of Care	Reduces error

Second order codes	First order codes
	Identifies priorities in patient care
	Improves on normal care
	Promotes pro-active disease management
	Better knowledge of patient's disease status
	Increases confidence in clinical decisions
	Provides education for staff
	Intervention feels important to staff
Empowers patients	Creates local champions to promote intervention
	Encourages patient self-care
	Increases patient knowledge

Healthcare staff negative experiences:

Second order codes	First order codes
Poor communication	Lack of patient to staff communication
	Lack of staff to staff communication
Does not improve clinical care	Reduces clinical care
	Increases staff errors
	No improvement in patient health status
	Lack of evidence for effectiveness
	No change in patient self-care
Disruptive to current practice	Increased workload
	Resistance to change
	Handing over responsibility of care causes anxiety
	Requires patients to be 'selected'
	Not linked with existing health records
Poor Design / Inaccessible to staff	High cost
	Medico-legal concerns
	Patient information security or privacy concerns
	Technical difficulties
	Not user friendly
	Poor staff computer literacy
	Lack of equipment or technical support
	Lack of training for intervention
	Lack of confidence in equipment and readings
Reduces patient independence	Perceived patient dependence on staff
	Lack of options/flexibility
	Intervention gives inflexible guidance
Poor Patient Education	Lack of education for the patient
	Increases patient confusion and concerns about condition

APPENDIX 9: FIRST ORDER CODE CONVERSIONS INTO THEMES (CHAPTER 2)

Communication	Clinical Care	Education	Ease of Use/ Accessibility	Freedom/ Convenience
		PATIENT EXPERIENCES		
Pt-staff communication	"feels looked after"	Clinical knowledge	User-Friendly	Saves travel time
Psychosocial support	Confidence in management decisions	Confidence/motivation in self-care	Popular	Comfort/ Freedom at home
Pt-Pt communication	Improvement from usual care	Involvement in self-care	New technology	Flexible
Lack of Pt-staff communication	Follow up/co-ordination of care	Lack of education	Not User Friendly	Lack of options
Lack of pt-pt communication	Lack of improvement	No effect on self-care	Cost	Extra work = tiring
	Lack of efficiency/ co-ordination	Lack of training	Lack of Privacy/ security	Responsibility = anxiety
	Unpredictable clinical management	Lack of feedback	Intrusive	Adds extra concern for carers
	Cannot replace hospital care	Irrelevant training	Technology overwhelming	Uncomfortable at home
	Lack of support for care	Unreliable information	Medical Jargon	Reliance on staff
	Extra work for clinicians		Lack of portability	Threat to independence/ control
			Technology not needed	
			Technical Difficulties	
			Language barriers	
		CARER EXPERIENCES		
	Feels patient is ‘looked after’	Informative/ educational	User friendly	Change is stressful
	Extra support	Lack of education	Invasion of privacy	Extra responsibility
	Lack of improvement		Technical difficulties = stressful	Causes concern for patient
			Not user friendly	Control taken away
			Technology not the solution	

Communication	Clinical Care	Education	Ease of Use/ Accessibility	Freedom/ Convenience
		HEALTHCARE STAFF EXPERIENCES		
Familiarity/ communication with patient	Confidence in management	Encourages patient self-care	Important	Automated saves time
Encourages teamwork	Better knowledge of patient status	Increases patient knowledge	User friendly	No change in workload
Local champions	Pro-active management	Staff education	Technical support	Saves travel time
Lack of patient- staff communication	Improvement from usual care	Lack of training	Security/ Privacy	Flexible to practice
Lack of staff-staff communication	Identifies priorities in care	Lack of education	Incentivisation	Increased workload
	Reduces error	No change in patient self-care	Cost savings	Slow to change practice
	Patient selection decisions		Lack of equipment/ support	Inflexible guidance
	Increases errors		Not user friendly	Increases patient concern/ confusion
	No improvement		Cost	Lack of options
	Health inequality		Technical difficulties	Clinician anxiety
	Limits clinical care		Not linked to records	Perceived dependence on staff
	Lack of evidence of effectiveness		Lack of confidence in equipment/ readings	Medico-legal concerns
			Computer literacy	
			Information privacy/ security	

APPENDIX 10: PARTICIPANT INFORMATION SHEET FOR DISCRETE CHOICE EXPERIMENT (CHAPTER 3)

Questionnaire on remote care in heart failure

Participant Information

Thank you for your interest in heart failure research.
This questionnaire is designed to find out which parts of remote care technology are most important for patients with heart failure.

Am I eligible?

To be eligible to complete this survey, you need to be over 18 and have been diagnosed with any form of long-term heart failure, including cardiomyopathy, infective or congenital causes.

What is Remote Care?

Remote care is the use of technology to help carry out medical care that would normally be available in a hospital or a clinic, but within your own home instead. Examples include a wireless blood pressure reader or a digital scale that sends readings directly to the doctor from your home. As medical technology continues to improve, remote care is becoming more common in medicine as a way to look after long-term health conditions from home. It helps care for patients that have trouble travelling to appointments, and can also alert doctors early if a patient needs more care, so that they can be treated quicker.

Why Heart Failure?

We have chosen patients with heart failure because this is a serious condition which often affects patients over a long period of time. Patients with heart failure often have other health conditions too, that make their care more complex so these patients would greatly benefit from improved health monitoring at home.

How will this survey help patients like me?

With the knowledge from this study, we can begin to design new technologies that suit heart failure patients better, so that they can continue to be used for longer and provide the greatest benefit for patients such as yourself. Remote care will soon have a much bigger role in medical care, and this research is an important way of bringing it closer to patients by finding out what your preferences are. The results of this study will directly help us create life-saving devices for heart failure, which could be used by you in the near future.

How do I complete the questionnaire?

The questionnaire will consist of 16 questions which should take no longer than 15 minutes to complete. You will be presented with an example of a remote care technology, and will be given two options that describe various features of the technology. For each question, you will be asked to pick which of the two technologies (A or B) you would prefer to use, based on the descriptions provided.

What will happen to my data?

All data is anonymised and confidential. This survey will not ask any personal questions or any information that could be used to identify you. The data will be stored on the online server for as long as the survey is open (3 months from the start date of the survey). The data will then be downloaded to a secure university account, which is only accessible by the researchers. As your information is fully anonymised, we unfortunately cannot contact you with the results of the study. However the study will be published on completion and you can visit our website below to find out any new project updates.

Who is conducting the study?

This study is supported by the University of Liverpool, UK and is funded by the Collaboration for Leadership in Applied Health Research and Care North West Coast (CLAHRC NWC) which is a part of the National Institute of Health Research (NIHR). This project is part of the Personalised Renal Monitoring via Information Technology (PERMIT) study. Find out more about the project here: http://tinyurl.com/NIHR-PERMIT
The main contact is Dr. Ahmed Al-Naher at the University of Liverpool. For further questions and enquiries, please contact: aalnaher@liverpool.ac.uk.

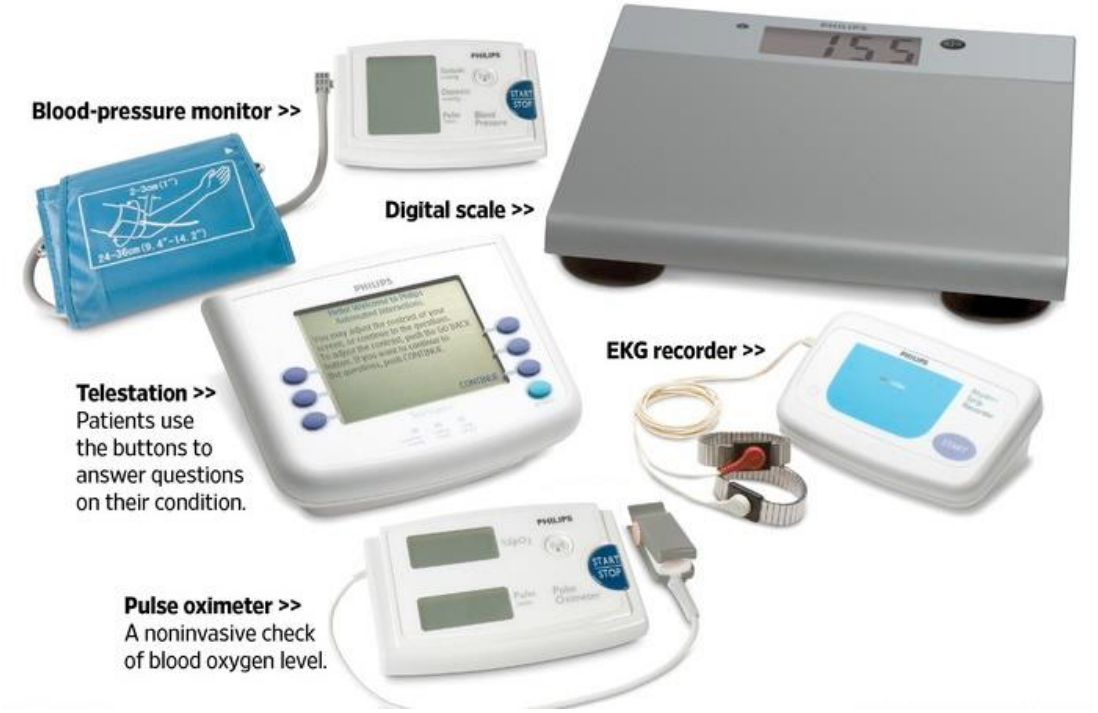
What is the PERMIT project?

Personalised Renal Monitoring via Information Technology (PERMIT) is a research project aimed to reduce the effects of kidney disease in heart failure. Unfortunately, patients with heart failure have a higher chance of developing problems with their kidney later on in life, and since this has no symptoms in the early stage, it is not often detected until it causes permanent kidney damage. PERMIT aims to create better guidelines for monitoring kidney health, to detect disease early and prevent damage that could lead to kidney failure. Developing remote care technology is a good way of detecting this damage at an early stage, and this study will help us achieve that.

APPENDIX 11: INSTRUCTIONS FOR ANSWERING QUESTIONNAIRE (CHAPTER 3)

How to answer this questionnaire

Imagine that you have been provided with a home monitoring system by your doctor to keep track of your health and manage your heart failure. A home monitoring system includes all of the following devices:



This system of devices is designed to allow you to take your own blood pressure, weight, oxygen level and heart rhythm at home, and track your symptoms. The readings are displayed on a website that you can use to send information back to your doctor to monitor your health.

This questionnaire is designed to find out which features of the home monitoring system are most important to you. Each of the following questions will describe two different versions of this home monitoring system. Please choose one of the two home monitoring systems you would most prefer to use.

Each question will include two options to choose from. Each option consists of 5 descriptions about the home monitoring system. This information will re-appear in each question, but will be different between the A and B choices, and in a different order each question. This is done on purpose to identify a pattern in your preferences, and see which technologies are more important to you than others.
As an example, in question 1, you will be presented with the two options in this way:

Example Question 1.

Which out of monitoring system A or B would you prefer?

	Monitoring system A	Monitoring system B
How often are measurements checked by your doctor, and how does this influence your care?	Frequent: used by your doctor to guide treatment	Infrequent: has no impact on the treatment you receive
Does the home monitoring system have a way to talk with or receive information directly from your doctor?	No	Yes
How long does it take each day to use, and send results to your doctor?	Long time	Quickly
How easy is the home monitoring system to use?	Very	Not at all
What feedback is given about your measurements, or information about your condition?	None	Some

Tick one: A) ☒ B) ☐

Please read the statements of both Monitoring System A and B carefully before deciding between which of the two you would prefer to use. Then select either A or B by ticking the appropriate box. There will be a total of 16 of these questions in total.

While it might feel like these questions are repetitive, they have been very carefully designed using scientific methods to get the most amount of information from your answers, which will in turn be very important for designing new technologies for heart failure patients. The questions become easier to answer the more you complete, and the questionnaire should take less than 10 mins in total. It is important that you complete all of these questions for your response to be counted. Your choices should reflect your personal preference only and so there are no wrong answers.

APPENDIX 12: DISCRETE CHOICE EXPERIMENT QUESTIONNAIRE (CHAPTER 3)

Questionnaire Start

Question 1.
Which out of monitoring system A or B would you prefer?

	Monitoring system A	Monitoring system B
How often are measurements checked by your doctor, and how does this influence your care?	Frequent: used by your doctor to guide treatment	Infrequent: has no impact on the treatment you receive
Does the home monitoring system have a way to talk with or receive information directly from your doctor?	No	Yes
How long does it take each day to use, and send results to your doctor?	Long time	Quickly
How easy is the home monitoring system to use?	Very	Not at all
What feedback is given about your measurements, or information about your condition?	None	Some

Tick one: A) ☐ B) ☐

Question 2.
Which out of monitoring system A or B would you prefer?

	Monitoring system A	Monitoring system B
How often are measurements checked by your doctor, and how does this influence your care?	Frequent: used by your doctor to guide treatment	Infrequent: has no impact on the treatment you receive
Does the home monitoring system have a way to talk with or receive information directly from your doctor?	No	Yes
How long does it take each day to use, and send results to your doctor?	Quickly	Long time
How easy is the home monitoring system to use?	Not at all	Very
What feedback is given about your measurements, or information about your condition?	None	Some

Tick one: A) ☐ B) ☐

Question 3.
Which out of monitoring system A or B would you prefer?

	Monitoring system A	Monitoring system B
How often are measurements checked by your doctor, and how does this influence your care?	Infrequent: has no impact on the treatment you receive	Frequent: used by your doctor to guide treatment
Does the home monitoring system have a way to talk with or receive information directly from your doctor?	No	Yes
How long does it take each day to use, and send results to your doctor?	Quickly	Long time
How easy is the home monitoring system to use?	Very	Not at all
What feedback is given about your measurements, or information about your condition?	None	Some

Tick one: A) ☐ B) ☐

Question 4.
Which out of monitoring system A or B would you prefer?

	Monitoring system A	Monitoring system B
How often are measurements checked by your doctor, and how does this influence your care?	Infrequent: has no impact on the treatment you receive	Frequent: used by your doctor to guide treatment
Does the home monitoring system have a way to talk with or receive information directly from your doctor?	Yes	No
How long does it take each day to use, and send results to your doctor?	Quickly	Long time
How easy is the home monitoring system to use?	Not at all	Very
What feedback is given about your measurements, or information about your condition?	None	Some

Tick one: A) ☐ B) ☐

Question 5.
Which out of monitoring system A or B would you prefer?

	Monitoring system A	Monitoring system B
How often are measurements checked by your doctor, and how does this influence your care?	Frequent: used by your doctor to guide treatment	Infrequent: has no impact on the treatment you receive
Does the home monitoring system have a way to talk with or receive information directly from your doctor?	Yes	No
How long does it take each day to use, and send results to your doctor?	Quickly	Long time
How easy is the home monitoring system to use?	Not at all	Very
What feedback is given about your measurements, or information about your condition?	Some	None

Tick one: A) ☐ B) ☐

Question 6.
Which out of monitoring system A or B would you prefer?

	Monitoring system A	Monitoring system B
How often are measurements checked by your doctor, and how does this influence your care?	Infrequent: has no impact on the treatment you receive	Frequent: used by your doctor to guide treatment
Does the home monitoring system have a way to talk with or receive information directly from your doctor?	No	Yes
How long does it take each day to use, and send results to your doctor?	Long time	Quickly
How easy is the home monitoring system to use?	Very	Not at all
What feedback is given about your measurements, or information about your condition?	Some	None

Tick one: A) ☐ B) ☐

Question 7.
Which out of monitoring system A or B would you prefer?

	Monitoring system A	Monitoring system B
How often are measurements checked by your doctor, and how does this influence your care?	Frequent: used by your doctor to guide treatment	Infrequent: has no impact on the treatment you receive
Does the home monitoring system have a way to talk with or receive information directly from your doctor?	Yes	No
How long does it take each day to use, and send results to your doctor?	Long time	Quickly
How easy is the home monitoring system to use?	Very	Not at all
What feedback is given about your measurements, or information about your condition?	None	Some

Tick one: A) ☐ B) ☐

Question 8.
Which out of monitoring system A or B would you prefer?

	Monitoring system A	Monitoring system B
How often are measurements checked by your doctor, and how does this influence your care?	Infrequent: has no impact on the treatment you receive	Frequent: used by your doctor to guide treatment
Does the home monitoring system have a way to talk with or receive information directly from your doctor?	Yes	No
How long does it take each day to use, and send results to your doctor?	Quickly	Long time
How easy is the home monitoring system to use?	Very	Not at all
What feedback is given about your measurements, or information about your condition?	Some	None

Tick one: A) ☐ B) ☐

Question 9.
Which out of monitoring system A or B would you prefer?

	Monitoring system A	Monitoring system B
How often are measurements checked by your doctor, and how does this influence your care?	Frequent: used by your doctor to guide treatment	Infrequent: has no impact on the treatment you receive
Does the home monitoring system have a way to talk with or receive information directly from your doctor?	No	Yes
How long does it take each day to use, and send results to your doctor?	Long time	Quickly
How easy is the home monitoring system to use?	Very	Not at all
What feedback is given about your measurements, or information about your condition?	None	Some

Tick one: A) ☐ B) ☐

Question 10.
Which out of monitoring system A or B would you prefer?

	Monitoring system A	Monitoring system B
How often are measurements checked by your doctor, and how does this influence your care?	Frequent: used by your doctor to guide treatment	Infrequent: has no impact on the treatment you receive
Does the home monitoring system have a way to talk with or receive information directly from your doctor?	Yes	No
How long does it take each day to use, and send results to your doctor?	Long time	Quickly
How easy is the home monitoring system to use?	Very	Not at all
What feedback is given about your measurements, or information about your condition?	Some	None

Tick one: A) ☐ B) ☐

Question 11.
Which out of monitoring system A or B would you prefer?

	Monitoring system A	Monitoring system B
How often are measurements checked by your doctor, and how does this influence your care?	Infrequent: has no impact on the treatment you receive	Frequent: used by your doctor to guide treatment
Does the home monitoring system have a way to talk with or receive information directly from your doctor?	Yes	No
How long does it take each day to use, and send results to your doctor?	Long time	Quickly
How easy is the home monitoring system to use?	Not at all	Very
What feedback is given about your measurements, or information about your condition?	Some	None

Tick one: A) ☐ B) ☐

Question 12.
Which out of monitoring system A or B would you prefer?

	Monitoring system A	Monitoring system B
How often are measurements checked by your doctor, and how does this influence your care?	Frequent: used by your doctor to guide treatment	Infrequent: has no impact on the treatment you receive
Does the home monitoring system have a way to talk with or receive information directly from your doctor?	No	Yes
How long does it take each day to use, and send results to your doctor?	Long time	Quickly
How easy is the home monitoring system to use?	Not at all	Very
What feedback is given about your measurements, or information about your condition?	Some	None

Tick one: A) ☐ B) ☐

Question 13.
Which out of monitoring system A or B would you prefer?

	Monitoring system A	Monitoring system B
How often are measurements checked by your doctor, and how does this influence your care?	Frequent: used by your doctor to guide treatment	Infrequent: has no impact on the treatment you receive
Does the home monitoring system have a way to talk with or receive information directly from your doctor?	No	Yes
How long does it take each day to use, and send results to your doctor?	Long time	Quickly
How easy is the home monitoring system to use?	Not at all	Very
What feedback is given about your measurements, or information about your condition?	None	Some

Tick one: A) ☐ B) ☐

Question 14.
Which out of monitoring system A or B would you prefer?

	Monitoring system A	Monitoring system B
How often are measurements checked by your doctor, and how does this influence your care?	Frequent: used by your doctor to guide treatment	Infrequent: has no impact on the treatment you receive
Does the home monitoring system have a way to talk with or receive information directly from your doctor?	No	Yes
How long does it take each day to use, and send results to your doctor?	Quickly	Long time
How easy is the home monitoring system to use?	Very	Not at all
What feedback is given about your measurements, or information about your condition?	Some	None

Tick one: A) ☐ B) ☐

Question 15.
Which out of monitoring system A or B would you prefer?

	Monitoring system A	Monitoring system B
How often are measurements checked by your doctor, and how does this influence your care?	Frequent: used by your doctor to guide treatment	Infrequent: has no impact on the treatment you receive
Does the home monitoring system have a way to talk with or receive information directly from your doctor?	No	Yes
How long does it take each day to use, and send results to your doctor?	Long time	Quickly
How easy is the home monitoring system to use?	Not at all	Very
What feedback is given about your measurements, or information about your condition?	Some	None

Tick one: A) ☐ B) ☐

Question 16.
Which out of monitoring system A or B would you prefer?

	Monitoring system A	Monitoring system B
How often are measurements checked by your doctor, and how does this influence your care?	Frequent: used by your doctor to guide treatment	Infrequent: has no impact on the treatment you receive
Does the home monitoring system have a way to talk with or receive information directly from your doctor?	Yes	No
How long does it take each day to use, and send results to your doctor?	Long time	Quickly
How easy is the home monitoring system to use?	Not at all	Very
What feedback is given about your measurements, or information about your condition?	None	Some

Tick one: A) ☐ B) ☐

Thank you for participating in this survey!

APPENDIX 13: READ CODES USED TO IDENTIFY PATIENTS WITH HEART FAILURE FROM SIR DATASET AS PART OF INCLUSION CRITERIA (CHAPTER 4)

ReadCode	Rubric
21264	Heart failure resolved
2126400	Heart failure resolved
14A6.	h/o: heart failure
14A6.00	h/o: heart failure
14AM.	h/o: heart failure in last year
14AM.00	h/o: heart failure in last year
1O1..	heart failure confirmed
1O1..00	Heart failure confirmed
388D.	new york heart assoc classification heart failure symptoms
388D.00	new york heart assoc classification heart failure symptoms
585f.	Echocardiogram shows left ventricular systolic dysfunction
585f.00	Echocardiogram shows left ventricular systolic dysfunction
661M5	heart failure self-management plan agreed
661M500	heart failure self-management plan agreed
662f	NYHA classification - class I
662f.	NYHA classification - class I
662f.00	NYHA I
662g	NYHA II
662g.	NYHA II
662g.00	NYHA II
662h	NYHA III
662h.	NYHA III
662h.00	NYHA III
662i	NYHA IV
662i.	NYHA IV
662i.00	NYHA IV
8B29.	cardiac failure therapy
8B29.00	cardiac failure therapy
8CeC.	preferred place of care for next exacerbation heart failure
8CeC.00	preferred place of care for next exacerbation heart failure
8CMK.	has heart failure management plan
8CMK.00	has heart failure management plan
8CMW8	heart failure clinical pathway
8CMW800	heart failure clinical pathway
8H2S.	Admit heart failure emergency
8H2S.00	Admit heart failure emergency

ReadCode	Rubric
9Or..	Heart Failure
G1yz1	Rheumatic left ventricular failure
G1yz100	Rheumatic left ventricular failure
G2101	malignant hypertensive heart disease with ccf
G210100	malignant hypertensive heart disease with ccf
G211100	benign hypertensive heart disease with ccf
G21z100	hypertensive heart disease nos with ccf
G232.00	hypertensive heart&renal dis wth (congestive) heart failure
G234.00	Hyperten heart&renal dis+both(congestv)heart and renal fail
G400.00	acute cor pulmonale
G41z.11	chronic cor pulmonale
G554000	congestive cardiomyopathy
G554011	congestive obstructive cardiomyopathy
G557100	beriberi heart disease
G58..	Heart failure
G58..00	Heart failure
G58..11	Cardiac failure
G580.	Heart failure
G5800	Heart failure
G5801	Chroncongestive heart failure
G5802	Decompensated cardiac failure
G5803	Compensated cardiac failure
G5804	Cong heart fail due valv dis
G580.00	Congestive heart failure
G580.11	Congestive cardiac failure
G580.12	Right heart failure
G580.13	Right ventricular failure
G580.14	Biventricular failure
G580000	Acute congestive heart failure
G580100	Chronic congestive heart failure
G580200	Decompensated cardiac failure
G580300	Compensated cardiac failure
G580400	Congestive heart failure due to valvular disease
G581	Heart failure
G581.	Heart failure
G581.00	Left ventricular failure
G5810	Acute left ventricular failure
G581.13	Impaired left ventricular function
G581000	Acute left ventricular failure
G582.00	Acute heart failure
G583.	Heart failure with normal ejection fraction
G583.00	Heart failure with normal ejection fraction

ReadCode	Rubric
G583.11	HFNEF - heart failure with normal ejection fraction
G583.12	Heart failure with preserved ejection fraction
G584.	Right ventricular failure
G584.00	Right ventricular failure
G58z.	Heart failure NOS
G58z.00	Heart failure NOS
G58z.12	Cardiac failure NOS
G5y4z	post cardiac operation heart failure nos
G5y4z00	post cardiac operation heart failure nos
G5yy9	Left ventricular systolic dysfunction
G5yy900	Left ventricular systolic dysfunction
G5yyD	Left ventricular cardiac dysfunction
G5yyD00	Left ventricular cardiac dysfunction
G5yyE	Right ventricular systolic dysfunction
G5yyE00	Right ventricular systolic dysfunction
R2y10	[d]cardiorespiratory failure
R2y1000	[d]cardiorespiratory failure
SP111	heart insuff. as a complication of care
SP11111	heart failure as a complication of care
ZRad.00	new york heart assoc classification heart failure symptoms

APPENDIX 14: READ CODES USED TO EXTRACT ALL CLINICAL VARIABLES FROM SIR DATA (CHAPTER 4)

Atrial Fibrillation:

ReadCode	Rubric
3272	ECG: atrial fibrillation
14AN	H/O: atrial fibrillation
G573	Atrial fibrillation and flutter
9Os	Atrial fibrillation monitoring administration
G573.	Atrial fibrillation and flutter
G573000	Atrial fibrillation and flutter
G573100	Atrial fibrillation
G5730	Atrial fibrillation
G573.00	Atrial fibrillation and flutter
G573200	Paroxysmal atrial fibrillation
G5732	Paroxysmal atrial fibrillation
G573300	Non-rheumatic atrial fibrillation
G5733	Non-rheumatic atrial fibrillation
G573400	Permanent atrial fibrillation
G5734	Permanent atrial fibrillation
G573500	Persistent atrial fibrillation
G5735	Persistent atrial fibrillation
G573600	Paroxysmal atrial flutter
G5736	Paroxysmal atrial flutter
G573700	Chronic atrial fibrillation
G573z00	Atrial fibrillation and flutter NOS
G573z	Atrial fibrillation and flutter NOS
9Os..	Atrial fibrillation monitoring administration
9Os0.	Atrial fibrillation monitoring first letter
9Os0	Atrial fibrillation monitoring first letter
9Os1.	Atrial fibrillation monitoring second letter
9Os1	Atrial fibrillation monitoring second letter
9Os2.	Atrial fibrillation monitoring third letter
9Os2	Atrial fibrillation monitoring third letter
9Os3.	Atrial fibrillation monitoring verbal invite
9Os3	Atrial fibrillation monitoring verbal invite
9Os4.	Atrial fibrillation monitoring telephone invite
9Os4	Atrial fibrillation monitoring telephone invite
3272	ECG: atrial fibrillation
14AN.	H/O: atrial fibrillation
662S.	Atrial fibrillation monitoring
6A9..00	Atrial fibrillation annual review
7936A00	Implant intravenous pacemaker for atrial fibrillation

ReadCode	Rubric
8CMW200	Atrial fibrillation care pathway
8HTy.00	Referral to atrial fibrillation clinic
8OAD.00	Provision of written information about atrial fibrillation
9Os..00	Atrial fibrillation monitoring administration
9Os0.00	Atrial fibrillation monitoring first letter
9Os1.00	Atrial fibrillation monitoring second letter
9Os2.00	Atrial fibrillation monitoring third letter
9Os3.00	Atrial fibrillation monitoring verbal invite
9Os4.00	Atrial fibrillation monitoring telephone invite

Blood Urea Nitrogen:

ReadCode	Rubric
44J9.	Serum urea level
44J9	Serum urea level
44J8.	Blood urea
44J8	Blood urea
44JA.	Plasma urea level
44JA	Plasma urea level
44J..00	Blood urea/renal function
44J8.00	Blood urea
44J8.11	Urea - blood
44J9.00	Serum urea level
44JA.00	Plasma urea level

BMI:

ReadCode	Rubric
229%	Height
22A%	Weight

BNP:

ReadCode	Rubric
44AX.	Serum B-type natriuretic peptide concentration
44AP.	Serum pro-brain natriuretic peptide level
44AN.	Plasma pro-brain natriuretic peptide level
44AW.	Plasma N-terminal pro B-type natriuretic peptide concentration
44AV.	Serum N-terminal pro B-type natriuretic peptide concentration

Chronic liver disease:

ReadCode	Rubric
ZV427	[V]Liver transplanted
ZV42700	[V]Liver transplanted
J6130	Alcoholic hepatic failure
J613000	Alcoholic hepatic failure
J614.	Chronic hepatitis
J614z	Chronic hepatitis NOS
J61z.	Chronic liver disease NOS
A7071	Chronic viral hepatitis B without delta-agent
A707100	Chronic viral hepatitis B without delta-agent
J615.	Cirrhosis - non alcoholic
J61..	Cirrhosis and chronic liver disease
J615z13	Cirrhosis Of Liver
J615z	Cirrhosis of liver NOS
C310400	Glycogenosis with hepatic cirrhosis
J62..	Liver abscess and sequelae of chronic liver disease
SP14211	Liver failure as a complication of care
J62y.	Liver failure NOS
J61yz	Other non-alcoholic chronic liver disease NOS

Creatinine:

ReadCode	Rubric
44J3.	Serum creatinine
44J3	Serum creatinine

Diabetes Mellitus:

ReadCode	Rubric
C100112	Non-insulin dependent diabetes mellitus
C10..	Diabetes mellitus
C10..00	Diabetes mellitus
C10F.00	Type 2 diabetes mellitus
C100011	Insulin dependent diabetes mellitus
C10FJ00	Insulin treated Type 2 diabetes mellitus
C10E.00	Type 1 diabetes mellitus
C10E2	Type 1 diabetes mellitus with neurological complications
C108.	Insulin dependent diabetes mellitus
C108.00	Insulin dependent diabetes mellitus
C101.	Diabetes mellitus with ketoacidosis
C101.00	Diabetes mellitus with ketoacidosis
66A4.	Diabetic on oral treatment
66A4.00	Diabetic on oral treatment

ReadCode	Rubric
F372.12	Diabetic neuropathy
66AJ.	Diabetic - poor control
66AJ.	Diabetic - poor control
66AJ.00	Diabetic - poor control
C104.11	Diabetic nephropathy
C104.11	Diabetic nephropathy
66AJ100	Brittle diabetes
66A..	Diabetic monitoring
66A..00	Diabetic monitoring
C109.	Non-insulin dependent diabetes mellitus
C109.00	Non-insulin dependent diabetes mellitus
F372.11	Diabetic polyneuropathy
C109.11	NIDDM - Non-insulin dependent diabetes mellitus
66AS.	Diabetic annual review
66AS.00	Diabetic annual review
C108700	Insulin dependent diabetes mellitus with retinopathy
C108800	Insulin dependent diabetes mellitus - poor control
66A3.	Diabetic on diet only
66A3.00	Diabetic on diet only
C106.12	Diabetes mellitus with neuropathy
C106.12	Diabetes mellitus with neuropathy
C109700	Non-insulin dependent diabetes mellitus - poor control
66AR.	Diabetes management plan given
66AR.00	Diabetes management plan given
66A5.	Diabetic on insulin
66A5.00	Diabetic on insulin
66AJ.	Unstable diabetes
66AJ.11	Unstable diabetes
9OL.	Diabetes monitoring admin.
9OL..00	Diabetes monitoring admin.
C10yy00	Other specified diabetes mellitus with other spec comps
C10ED00	Type 1 diabetes mellitus with nephropathy
C10EM00	Type 1 diabetes mellitus with ketoacidosis
66Ac.	Diabetic peripheral neuropathy screening
66Ac.00	Diabetic peripheral neuropathy screening
66AH000	Conversion to insulin
C10B.	Diabetes mellitus induced by steroids
C10B.00	Diabetes mellitus induced by steroids
9OL6.	Diabetes monitoring 3rd letter
9OL6.00	Diabetes monitoring 3rd letter
66AU.	Diabetes care by hospital only
66AU.00	Diabetes care by hospital only
C10E.11	Type I diabetes mellitus
66AP.	Diabetes: practice programme
66AP.00	Diabetes: practice programme

ReadCode	Rubric
C10FC00	Type 2 diabetes mellitus with nephropathy
66AQ.	Diabetes: shared care programme
66AQ.00	Diabetes: shared care programme
C10F500	Type 2 diabetes mellitus with gangrene
66AZ.	Diabetic monitoring NOS
66AZ.00	Diabetic monitoring NOS
66A8.	Has seen dietician - diabetes
66A8.00	Has seen dietician - diabetes
66AI.	Diabetic - good control
66AI.00	Diabetic - good control
9OL4.	Diabetes monitoring 1st letter
9OL4.00	Diabetes monitoring 1st letter
9OL5.	Diabetes monitoring 2nd letter
9OL5.00	Diabetes monitoring 2nd letter
66AD.	Fundoscopy - diabetic check
66AD.00	Fundoscopy - diabetic check
C104y00	Other specified diabetes mellitus with renal complications
66A7.	Frequency of hypo. attacks
66A7.00	Frequency of hypo. attacks
C100100	Diabetes mellitus, adult onset, no mention of complication
C100111	Maturity onset diabetes
C314.	Renal diabetes
C103.	Diabetes mellitus with ketoacidotic coma
C103.00	Diabetes mellitus with ketoacidotic coma
C106.	Diabetes mellitus with neurological manifestation
C106.00	Diabetes mellitus with neurological manifestation
66AH.00	Diabetic treatment changed
66AH.00	Diabetic treatment changed
C106.13	Diabetes mellitus with polyneuropathy
C106.13	Diabetes mellitus with polyneuropathy
C104.	Diabetes mellitus with renal manifestation
C104.00	Diabetes mellitus with renal manifestation
2G5A.	O/E - Right diabetic foot at risk
2G5A.00	O/E - Right diabetic foot at risk
C109600	Non-insulin-dependent diabetes mellitus with retinopathy
C108F11	Type I diabetes mellitus with diabetic cataract
C108.12	Type 1 diabetes mellitus
C109.12	Type 2 diabetes mellitus
66AL.	Diabetic-uncooperative patient
66AL.00	Diabetic-uncooperative patient
66AM.	Diabetic - follow-up default
66AM.00	Diabetic - follow-up default
2G5C.	Foot abnormality - diabetes related
2G5C.00	Foot abnormality - diabetes related
C109G11	Type II diabetes mellitus with arthropathy

ReadCode	Rubric
66AT.	Annual diabetic blood test
66AT.00	Annual diabetic blood test
C109012	Type 2 diabetes mellitus with renal complications
C109.13	Type II diabetes mellitus
C108J12	Type 1 diabetes mellitus with neuropathic arthropathy
C109J12	Insulin treated Type II diabetes mellitus
C109J00	Insulin treated Type 2 diabetes mellitus
C10E700	Type 1 diabetes mellitus with retinopathy
C10FM00	Type 2 diabetes mellitus with persistent microalbuminuria
C10FB00	Type 2 diabetes mellitus with polyneuropathy
C10F600	Type 2 diabetes mellitus with retinopathy
C108.11	IDDM-Insulin dependent diabetes mellitus
C10EH00	Type 1 diabetes mellitus with arthropathy
C10E500	Type 1 diabetes mellitus with ulcer
C10F000	Type 2 diabetes mellitus with renal complications
66AA.11	Injection sites - diabetic
C102.	Diabetes mellitus with hyperosmolar coma
C102.00	Diabetes mellitus with hyperosmolar coma
C108012	Type 1 diabetes mellitus with renal complications
66AJz00	Diabetic - poor control NOS
C10N.	Secondary diabetes mellitus
C10N.00	Secondary diabetes mellitus
C106z00	Diabetes mellitus NOS with neurological manifestation
66Ab.	Diabetic foot examination
66Ab.00	Diabetic foot examination
C10EP00	Type 1 diabetes mellitus with exudative maculopathy
C10F.11	Type II diabetes mellitus
66AJ000	Chronic hyperglycaemia
C108.13	Type I diabetes mellitus
C109711	Type II diabetes mellitus - poor control
C100000	Diabetes mellitus, juvenile type, no mention of complication
F372200	Asymptomatic diabetic neuropathy
C109G00	Non-insulin dependent diabetes mellitus with arthropathy
C108B00	Insulin dependent diabetes mellitus with mononeuropathy
C109C12	Type 2 diabetes mellitus with nephropathy
C10FQ00	Type 2 diabetes mellitus with exudative maculopathy
C10F700	Type 2 diabetes mellitus - poor control
66Aa.	Diabetic diet - poor compliance
66Aa.00	Diabetic diet - poor compliance
C10FL00	Type 2 diabetes mellitus with persistent proteinuria
C10B000	Steroid induced diabetes mellitus without complication
66AY.	Diabetic diet - good compliance
66AY.00	Diabetic diet - good compliance
2G5B.	O/E - Left diabetic foot at risk
2G5B.00	O/E - Left diabetic foot at risk

ReadCode	Rubric
2G5E.	O/E - Right diabetic foot at low risk
2G5E.00	O/E - Right diabetic foot at low risk
2G5I.	O/E - Left diabetic foot at low risk
2G5I.00	O/E - Left diabetic foot at low risk
C108400	Unstable insulin dependent diabetes mellitus
2G51000	Foot abnormality - diabetes related
66AV.	Diabetic on insulin and oral treatment
66AV.00	Diabetic on insulin and oral treatment
66Ai.	Diabetic 6 month review
66Ai.00	Diabetic 6 month review
66AN.	Date diabetic treatment start
66AN.00	Date diabetic treatment start
C109900	Non-insulin-dependent diabetes mellitus without complication
C10EL00	Type 1 diabetes mellitus with persistent microalbuminuria
C10EK00	Type 1 diabetes mellitus with persistent proteinuria
2G5J.	O/E - Left diabetic foot at moderate risk
2G5J.00	O/E - Left diabetic foot at moderate risk
2G5F.	O/E - Right diabetic foot at moderate risk
2G5F.00	O/E - Right diabetic foot at moderate risk
2G5G.	O/E - Right diabetic foot at high risk
2G5G.00	O/E - Right diabetic foot at high risk
2G5K.	O/E - Left diabetic foot at high risk
2G5K.00	O/E - Left diabetic foot at high risk
9OL7.	Diabetes monitor.verbal invite
9OL7.00	Diabetes monitor.verbal invite
C108900	Insulin dependent diabetes maturity onset
66A7000	Frequency of hospital treated hypoglycaemia
F372.	Polyneuropathy in diabetes
F372.00	Polyneuropathy in diabetes
C107.11	Diabetes mellitus with gangrene
C107.12	Diabetes with gangrene
66Af.	Patient diabetes education review
66Af.00	Patient diabetes education review
C10FN00	Type 2 diabetes mellitus with ketoacidosis
C105.	Diabetes mellitus with ophthalmic manifestation
C105.00	Diabetes mellitus with ophthalmic manifestation
C10y.	Diabetes mellitus with other specified manifestation
C10y.00	Diabetes mellitus with other specified manifestation
C107200	Diabetes mellitus, adult with gangrene
C10A100	Malnutrition-related diabetes mellitus with ketoacidosis
G73y0	Diabetic peripheral angiopathy
C10F200	Type 2 diabetes mellitus with neurological complications
C105z00	Diabetes mellitus NOS with ophthalmic manifestation
C10FK00	Hyperosmolar non-ketotic state in type 2 diabetes mellitus
C109400	Non-insulin dependent diabetes mellitus with ulcer

ReadCode	Rubric
C104100	Diabetes mellitus, adult onset, with renal manifestation
C104z00	Diabetes mellitus with nephropathy NOS
2G5L.	O/E - Left diabetic foot - ulcerated
2G5L.00	O/E - Left diabetic foot - ulcerated
C10E800	Type 1 diabetes mellitus - poor control
2G5H.	O/E - Right diabetic foot - ulcerated
2G5H.00	O/E - Right diabetic foot - ulcerated
C10FH00	Type 2 diabetes mellitus with neuropathic arthropathy
C107.	Diabetes mellitus with peripheral circulatory disorder
C107.00	Diabetes mellitus with peripheral circulatory disorder
F372100	Chronic painful diabetic neuropathy
C109K00	Hyperosmolar non-ketotic state in type 2 diabetes mellitus
C10D.	Diabetes mellitus autosomal dominant type 2
C10D.00	Diabetes mellitus autosomal dominant type 2
C109J11	Insulin treated non-insulin dependent diabetes mellitus
C10FF00	Type 2 diabetes mellitus with peripheral angiopathy
66A9.	Understands diet - diabetes
66A9.00	Understands diet - diabetes
C108711	Type I diabetes mellitus with retinopathy
C101y00	Other specified diabetes mellitus with ketoacidosis
C1.	Diabetes mellitus with no mention of complication
C100.00	Diabetes mellitus with no mention of complication
C10EE00	Type 1 diabetes mellitus with hypoglycaemic coma
C106100	Diabetes mellitus, adult onset, + neurological manifestation
C108J00	Insulin dependent diab mell with neuropathic arthropathy
C102000	Diabetes mellitus, juvenile type, with hyperosmolar coma
66A7100	Frequency of GP or paramedic treated hypoglycaemia
C109500	Non-insulin dependent diabetes mellitus with gangrene
C10E900	Type 1 diabetes mellitus maturity onset
C10EN00	Type 1 diabetes mellitus with ketoacidotic coma
C109H00	Non-insulin dependent d m with neuropathic arthropathy
C108712	Type 1 diabetes mellitus with retinopathy
C105100	Diabetes mellitus, adult onset, + ophthalmic manifestation
C108C00	Insulin dependent diabetes mellitus with polyneuropathy
C101z00	Diabetes mellitus NOS with ketoacidosis
C103000	Diabetes mellitus, juvenile type, with ketoacidotic coma
C108E11	Type I diabetes mellitus with hypoglycaemic coma
C109612	Type 2 diabetes mellitus with retinopathy
C10E200	Type 1 diabetes mellitus with neurological complications
C102100	Diabetes mellitus, adult onset, with hyperosmolar coma
C10F311	Type II diabetes mellitus with multiple complications
C10C.	Diabetes mellitus autosomal dominant
C10C.00	Diabetes mellitus autosomal dominant
C109D00	Non-insulin dependent diabetes mellitus with hypoglyca coma
C10M.	Lipoatrophic diabetes mellitus

ReadCode	Rubric
C10M.00	Lipoatrophic diabetes mellitus
C10E400	Unstable type 1 diabetes mellitus
66AK.	Diabetic - cooperative patient
66AK.00	Diabetic - cooperative patient
C108F00	Insulin dependent diabetes mellitus with diabetic cataract
C108E00	Insulin dependent diabetes mellitus with hypoglycaemic coma
C108500	Insulin dependent diabetes mellitus with ulcer
C109E12	Type 2 diabetes mellitus with diabetic cataract
C10FE00	Type 2 diabetes mellitus with diabetic cataract
C10E312	Insulin dependent diabetes mellitus with multiple complicat
C109B00	Non-insulin dependent diabetes mellitus with polyneuropathy
C10z.	Diabetes mellitus with unspecified complication
C10z.00	Diabetes mellitus with unspecified complication
C109712	Type 2 diabetes mellitus - poor control
C108812	Type 1 diabetes mellitus - poor control
C109212	Type 2 diabetes mellitus with neurological complications
C109512	Type 2 diabetes mellitus with gangrene
C108y00	Other specified diabetes mellitus with multiple comps
C10EC00	Type 1 diabetes mellitus with polyneuropathy
66AX.	Diabetes: shared care in pregnancy - diabetol and obstet
66AX.00	Diabetes: shared care in pregnancy - diabetol and obstet
C10C.11	Maturity onset diabetes in youth
C108811	Type I diabetes mellitus - poor control
C10FD00	Type 2 diabetes mellitus with hypoglycaemic coma
C108000	Insulin-dependent diabetes mellitus with renal complications
C10F711	Type II diabetes mellitus - poor control
C10F100	Type 2 diabetes mellitus with ophthalmic complications
C105y00	Other specified diabetes mellitus with ophthalmic complicatn
C109B11	Type II diabetes mellitus with polyneuropathy
C10E000	Type 1 diabetes mellitus with renal complications
C10E100	Type 1 diabetes mellitus with ophthalmic complications
C10E300	Type 1 diabetes mellitus with multiple complications
C109H11	Type II diabetes mellitus with neuropathic arthropathy
C10F900	Type 2 diabetes mellitus without complication
F372000	Acute painful diabetic neuropathy
C109E11	Type II diabetes mellitus with diabetic cataract
C10F400	Type 2 diabetes mellitus with ulcer
C108211	Type I diabetes mellitus with neurological complications
C108100	Insulin-dependent diabetes mellitus with ophthalmic comps
C10EF00	Type 1 diabetes mellitus with diabetic cataract
2G5W.	O/E - left chronic diabetic foot ulcer
2G5W.00	O/E - left chronic diabetic foot ulcer
C10F611	Type II diabetes mellitus with retinopathy
C109G12	Type 2 diabetes mellitus with arthropathy
C10E411	Unstable type I diabetes mellitus

ReadCode	Rubric
66AW.	Diabetic foot risk assessment
66AW.00	Diabetic foot risk assessment
C109011	Type II diabetes mellitus with renal complications
C109100	Non-insulin-dependent diabetes mellitus with ophthalm comps
C10FB11	Type II diabetes mellitus with polyneuropathy
C109A11	Type II diabetes mellitus with mononeuropathy
C100z00	Diabetes mellitus NOS with no mention of complication
C10E.12	Insulin dependent diabetes mellitus
C10G.	Secondary pancreatic diabetes mellitus
C10G.00	Secondary pancreatic diabetes mellitus
C10FP00	Type 2 diabetes mellitus with ketoacidotic coma
C108511	Type I diabetes mellitus with ulcer
C108300	Insulin dependent diabetes mellitus with multiple complicatn
C10A.	Malnutrition-related diabetes mellitus
C10A.00	Malnutrition-related diabetes mellitus
C108200	Insulin-dependent diabetes mellitus with neurological comps
C109000	Non-insulin-dependent diabetes mellitus with renal comps
C101000	Diabetes mellitus, juvenile type, with ketoacidosis
66AG.	Diabetic drug side effects
66AG.00	Diabetic drug side effects
C10F911	Type II diabetes mellitus without complication
C10EJ00	Type 1 diabetes mellitus with neuropathic arthropathy
C109F00	Non-insulin-dependent d m with peripheral angiopath
C10E412	Unstable insulin dependent diabetes mellitus
C101100	Diabetes mellitus, adult onset, with ketoacidosis
C109F11	Type II diabetes mellitus with peripheral angiopathy
C109411	Type II diabetes mellitus with ulcer
C10EQ00	Type 1 diabetes mellitus with gastroparesis
C109200	Non-insulin-dependent diabetes mellitus with neuro comps
C109D11	Type II diabetes mellitus with hypoglycaemic coma
C108A00	Insulin-dependent diabetes without complication
C107400	NIDDM with peripheral circulatory disorder
C10F011	Type II diabetes mellitus with renal complications
C108D00	Insulin dependent diabetes mellitus with nephropathy
C109611	Type II diabetes mellitus with retinopathy
C10FG00	Type 2 diabetes mellitus with arthropathy
C103y00	Other specified diabetes mellitus with coma
C109C00	Non-insulin dependent diabetes mellitus with nephropathy
C109111	Type II diabetes mellitus with ophthalmic complications
C106.11	Diabetic amyotrophy
C106.11	Diabetic amyotrophy
C10D.11	Maturity onset diabetes in youth type 2
C108411	Unstable type I diabetes mellitus
C108J11	Type I diabetes mellitus with neuropathic arthropathy
C108600	Insulin dependent diabetes mellitus with gangrene

ReadCode	Rubric
C109F12	Type 2 diabetes mellitus with peripheral angiopathy
C10FL11	Type II diabetes mellitus with persistent proteinuria
C109D12	Type 2 diabetes mellitus with hypoglycaemic coma
C10H.	Diabetes mellitus induced by non-steroid drugs
C10H.00	Diabetes mellitus induced by non-steroid drugs
C108011	Type I diabetes mellitus with renal complications
66Al.	Diabetic monitoring - higher risk albumin excretion
66Al.00	Diabetic monitoring - higher risk albumin excretion
C106y00	Other specified diabetes mellitus with neurological comps
C108212	Type 1 diabetes mellitus with neurological complications
C109511	Type II diabetes mellitus with gangrene
C109300	Non-insulin-dependent diabetes mellitus with multiple comps
C10EM11	Type I diabetes mellitus with ketoacidosis
C108H11	Type I diabetes mellitus with arthropathy
C10EA11	Type I diabetes mellitus without complication
C10FA00	Type 2 diabetes mellitus with mononeuropathy
C108911	Type I diabetes mellitus maturity onset
C107100	Diabetes mellitus, adult, + peripheral circulatory disorder
C10y100	Diabetes mellitus, adult, + other specified manifestation
C10FR00	Type 2 diabetes mellitus with gastroparesis
C10z100	Diabetes mellitus, adult onset, + unspecified complication
C10zy00	Other specified diabetes mellitus with unspecified comps
C10zz00	Diabetes mellitus NOS with unspecified complication
C108G00	Insulin dependent diab mell with peripheral angiopathy
C108z00	Unspecified diabetes mellitus with multiple complications
C109C11	Type II diabetes mellitus with nephropathy
C10FJ11	Insulin treated Type II diabetes mellitus
C107z00	Diabetes mellitus NOS with peripheral circulatory disorder
C103z00	Diabetes mellitus NOS with ketoacidotic coma
C10F300	Type 2 diabetes mellitus with multiple complications
C108H00	Insulin dependent diabetes mellitus with arthropathy
C109412	Type 2 diabetes mellitus with ulcer
C10EN11	Type I diabetes mellitus with ketoacidotic coma
66Ah.	Insulin needles changed for each injection
66Ah.00	Insulin needles changed for each injection
66Ak.	Diabetic monitoring - lower risk albumin excretion
66Ak.00	Diabetic monitoring - lower risk albumin excretion
C10A000	Malnutrition-related diabetes mellitus with coma
C108D11	Type I diabetes mellitus with nephropathy
C109H12	Type 2 diabetes mellitus with neuropathic arthropathy
C10H000	DM induced by non-steroid drugs without complication
C106000	Diabetes mellitus, juvenile, + neurological manifestation
C109211	Type II diabetes mellitus with neurological complications
C10EB00	Type 1 diabetes mellitus with mononeuropathy
C108512	Type 1 diabetes mellitus with ulcer

ReadCode	Rubric
C10J.	Insulin autoimmune syndrome
C10J.00	Insulin autoimmune syndrome
C10z000	Diabetes mellitus, juvenile type, + unspecified complication
C103100	Diabetes mellitus, adult onset, with ketoacidotic coma
C107300	IDDM with peripheral circulatory disorder
66Aj.	Insulin needles changed less than once a day
66Aj.00	Insulin needles changed less than once a day
C109E00	Non-insulin depend diabetes mellitus with diabetic cataract
C10EA00	Type 1 diabetes mellitus without complication
C105000	Diabetes mellitus, juvenile type, + ophthalmic manifestation
C10E600	Type 1 diabetes mellitus with gangrene
C109112	Type 2 diabetes mellitus with ophthalmic complications
C107000	Diabetes mellitus, juvenile +peripheral circulatory disorder
C108E12	Type 1 diabetes mellitus with hypoglycaemic coma
C10yz00	Diabetes mellitus NOS with other specified manifestation
C109A00	Non-insulin dependent diabetes mellitus with mononeuropathy
C102z00	Diabetes mellitus NOS with hyperosmolar coma
C10E812	Insulin dependent diabetes mellitus - poor control
66Am.	Insulin dose changed
66Am.00	Insulin dose changed
66Ao.	Diabetes type 2 review
66Ao.00	Diabetes type 2 review
66An.	Diabetes type 1 review
66An.00	Diabetes type 1 review
C10FM11	Type II diabetes mellitus with persistent microalbuminuria
C10F411	Type II diabetes mellitus with ulcer
C10E311	Type I diabetes mellitus with multiple complications
C10EC11	Type I diabetes mellitus with polyneuropathy
C10N100	Cystic fibrosis related diabetes mellitus
C10EG00	Type 1 diabetes mellitus with peripheral angiopathy
C10FE11	Type II diabetes mellitus with diabetic cataract
C10E712	Insulin dependent diabetes mellitus with retinopathy
C10E511	Type I diabetes mellitus with ulcer
C104000	Diabetes mellitus, juvenile type, with renal manifestation
C10N000	Secondary diabetes mellitus without complication
C10E711	Type I diabetes mellitus with retinopathy
C10FA11	Type II diabetes mellitus with mononeuropathy
C10FS00	Maternally inherited diabetes mellitus
C10ER00	Latent autoimmune diabetes mellitus in adult
C108A11	Type I diabetes mellitus without complication
66Aq.	Diabetic foot screen
66Aq.00	Diabetic foot screen
66Ap.	Insulin treatment initiated
66Ap.00	Insulin treatment initiated
C10E911	Type I diabetes mellitus maturity onset

ReadCode	Rubric
C10G000	Secondary pancreatic diabetes mellitus without complication
C108912	Type 1 diabetes mellitus maturity onset
C108412	Unstable type 1 diabetes mellitus
C10E912	Insulin dependent diabetes maturity onset
C10EP11	Type I diabetes mellitus with exudative maculopathy
C10E112	Insulin-dependent diabetes mellitus with ophthalmic comps
C10C.12	Maturity onset diabetes in youth type 1
C10F211	Type II diabetes mellitus with neurological complications
C10E512	Insulin dependent diabetes mellitus with ulcer
C10FD11	Type II diabetes mellitus with hypoglycaemic coma
C108B11	Type I diabetes mellitus with mononeuropathy
C10E111	Type I diabetes mellitus with ophthalmic complications
C10EE12	Insulin dependent diabetes mellitus with hypoglycaemic coma
C10EA12	Insulin-dependent diabetes without complication
C10A500	Malnutritn-relat diabetes melitus wth periph circul complctn
C10EF12	Insulin dependent diabetes mellitus with diabetic cataract
C10F111	Type II diabetes mellitus with ophthalmic complications
66At.	Diabetic dietary review
66At.00	Diabetic dietary review
C10EC12	Insulin dependent diabetes mellitus with polyneuropathy
66As.	Diabetic on subcutaneous treatment
66As.00	Diabetic on subcutaneous treatment
C10E212	Insulin-dependent diabetes mellitus with neurological comps
66At100	Type II diabetic dietary review
C10E611	Type I diabetes mellitus with gangrene
C10ED12	Insulin dependent diabetes mellitus with nephropathy
C10FC11	Type II diabetes mellitus with nephropathy
66Au.	Diabetic erectile dysfunction review
66Au.00	Diabetic erectile dysfunction review
66Av.	Diabetic assessment of erectile dysfunction
66Av.00	Diabetic assessment of erectile dysfunction
66Aw.	Insulin dose
66Aw.00	Insulin dose
66At111	Type 2 diabetic dietary review
C10EL11	Type I diabetes mellitus with persistent microalbuminuria
66At000	Type I diabetic dietary review
C108112	Type 1 diabetes mellitus with ophthalmic complications
C10E012	Insulin-dependent diabetes mellitus with renal complications
C10FG11	Type II diabetes mellitus with arthropathy
C10F511	Type II diabetes mellitus with gangrene
66At011	Type 1 diabetic dietary review
C10FF11	Type II diabetes mellitus with peripheral angiopathy
C10E811	Type I diabetes mellitus - poor control
2G5d.	O/E - Left diabetic foot at increased risk
2G5d.00	O/E - Left diabetic foot at increased risk

ReadCode	Rubric
2G5e.	O/E - Right diabetic foot at increased risk
2G5e.00	O/E - Right diabetic foot at increased risk
C109912	Type 2 diabetes mellitus without complication
C10FP11	Type 2 diabetes mellitus with ketoacidotic coma
C10FP11	Type II diabetes mellitus with ketoacidotic coma
C10FN11	Type II diabetes mellitus with ketoacidosis
66AH100	Conversion to insulin in secondary care
66AS000	Diabetes Year of Care annual review
66AH200	Conversion to insulin by diabetes specialist nurse
C10FK11	Hyperosmolar non-ketotic state in type II diabetes mellitus
C10P100	Type II diabetes mellitus in remission
C109312	Type 2 diabetes mellitus with multiple complications
C108311	Type I diabetes mellitus with multiple complications
C10EQ11	Type I diabetes mellitus with gastroparesis
C10E612	Insulin dependent diabetes mellitus with gangrene
C109911	Type II diabetes mellitus without complication
C10FH11	Type II diabetes mellitus with neuropathic arthropathy
C10E011	Type I diabetes mellitus with renal complications
C109B12	Type 2 diabetes mellitus with polyneuropathy
66AJ1	Brittle diabetes
66AJ2	Loss of hypoglycaemic warning
66AJz	Diabetic - poor control NOS
C10A0	Malnutrition-related diabetes mellitus with coma
C10A1	Malnutrition-related diabetes mellitus with ketoacidosis
C10A2	Malnutrition-related diabetes mellitus with renal complications
C10A3	Malnutrition-related diabetes mellitus with ophthalmic complications
C10A4	Malnutrition-related diabetes mellitus with neurological complications
C10A5	Malnutrition-related diabetes mellitus with peripheral circulatory complications
C10A6	Malnutrition-related diabetes mellitus with multiple complications
C10A7	Malnutrition-related diabetes mellitus without complications
C10AW	Malnutrition-related diabetes mellitus with unspecified complications
C10AX	Malnutrition-related diabetes mellitus with other specified complications
C10B0	Steroid induced diabetes mellitus without complication
C10E.	Type 1 diabetes mellitus
C10E0	Type 1 diabetes mellitus with renal complications
C10E1	Type 1 diabetes mellitus with ophthalmic complications
C10E3	Type 1 diabetes mellitus with multiple complications
C10E4	Unstable type 1 diabetes mellitus
C10E5	Type 1 diabetes mellitus with ulcer
C10E6	Type 1 diabetes mellitus with gangrene
C10E7	Type 1 diabetes mellitus with retinopathy
C10E8	Type 1 diabetes mellitus - poor control
C10E9	Type 1 diabetes mellitus maturity onset
C10EA	Type 1 diabetes mellitus without complication

ReadCode	Rubric
C10EB	Type 1 diabetes mellitus with mononeuropathy
C10EC	Type 1 diabetes mellitus with polyneuropathy
C10ED	Type 1 diabetes mellitus with nephropathy
C10EE	Type 1 diabetes mellitus with hypoglycaemic coma
C10EF	Type 1 diabetes mellitus with diabetic cataract
C10EG	Type 1 diabetes mellitus with peripheral angiopathy
C10EH	Type 1 diabetes mellitus with arthropathy
C10EJ	Type 1 diabetes mellitus with neuropathic arthropathy
C10EK	Type 1 diabetes mellitus with persistent proteinuria
C10EL	Type 1 diabetes mellitus with persistent microalbuminuria
C10EM	Type 1 diabetes mellitus with ketoacidosis
C10EN	Type 1 diabetes mellitus with ketoacidotic coma
C10EP	Type 1 diabetes mellitus with exudative maculopathy
C10EQ	Type 1 diabetes mellitus with gastroparesis
C10ER	Latent autoimmune diabetes mellitus in adult
C10F.	Type 2 diabetes mellitus
C10F0	Type 2 diabetes mellitus with renal complications
C10F1	Type 2 diabetes mellitus with ophthalmic complications
C10F2	Type 2 diabetes mellitus with neurological complications
C10F3	Type 2 diabetes mellitus with multiple complications
C10F4	Type 2 diabetes mellitus with ulcer
C10F5	Type 2 diabetes mellitus with gangrene
C10F6	Type 2 diabetes mellitus with retinopathy
C10F7	Type 2 diabetes mellitus - poor control
C10F9	Type 2 diabetes mellitus without complication
C10FA	Type 2 diabetes mellitus with mononeuropathy
C10FB	Type 2 diabetes mellitus with polyneuropathy
C10FC	Type 2 diabetes mellitus with nephropathy
C10FD	Type 2 diabetes mellitus with hypoglycaemic coma
C10FE	Type 2 diabetes mellitus with diabetic cataract
C10FF	Type 2 diabetes mellitus with peripheral angiopathy
C10FG	Type 2 diabetes mellitus with arthropathy
C10FH	Type 2 diabetes mellitus with neuropathic arthropathy
C10FJ	Insulin treated Type 2 diabetes mellitus
C10FK	Hyperosmolar non-ketotic state in type 2 diabetes mellitus
C10FL	Type 2 diabetes mellitus with persistent proteinuria
C10FM	Type 2 diabetes mellitus with persistent microalbuminuria
C10FN	Type 2 diabetes mellitus with ketoacidosis
C10FQ	Type 2 diabetes mellitus with exudative maculopathy
C10FR	Type 2 diabetes mellitus with gastroparesis
C10FS	Maternally inherited diabetes mellitus
F3720	Acute painful diabetic neuropathy
F3721	Chronic painful diabetic neuropathy
F3722	Asymptomatic diabetic neuropathy

Dialysis or renal replacement therapy:

ReadCode	Rubric
14V2	H/O: renal dialysis
14V2.	H/O: renal dialysis
14V2.00	H/O: renal dialysis
14V2.11	H/O: kidney dialysis
4N0..00	Dialysis fluid urea level
4N2..00	Dialysis fluid glucose level
7L1A	Compensation for renal failure
7L1A.	Compensation for renal failure
7L1A.00	Compensation for renal failure
7L1a.00	Cognitive behavioural therapy
7L1A.11	Dialysis for renal failure
7L1A000	Renal dialysis
7L1A011	Thomas intravascular shunt for dialysis
7L1A100	Peritoneal dialysis
7L1A200	Haemodialysis NEC
7L1A300	Haemofiltration
7L1A400	Automated peritoneal dialysis
7L1A500	Continuous ambulatory peritoneal dialysis
7L1A600	Peritoneal dialysis NEC
8DD	Dependence on renal dialysis
8DD..	Dependence on renal dialysis
8DE	Dialysis therapy started by renal service
8DE..	Dialysis therapy started by renal service
8DF	Dialysis therapy stopped by renal service
8DF..	Dialysis therapy stopped by renal service
SP0E	Disorders associated with peritoneal dialysis
SP0E.	Disorders associated with peritoneal dialysis
SP0E.00	Disorders associated with peritoneal dialysis
SP0F	Haemodialysis first use syndrome
SP0F.	Haemodialysis first use syndrome
SP0F.00	Haemodialysis first use syndrome
SP0H	Disorder associated with dialysis
SP0H.	Disorder associated with dialysis
SP0H0	Dialysis disequilibrium
ZV451	[V]Renal dialysis status
ZV45100	[V]Renal dialysis status
ZVu3G	[X]Other dialysis
ZVu3G00	[X]Other dialysis
4I29.00	peritoneal dialysis sample
7A60.00	arteriovenous shunt
7A60000	insertion of arteriovenous prosthesis
7A60100	creation of arteriovenous fistula nec
7A60111	creation of radial-cephalic fistula

ReadCode	Rubric
7A60112	creation of brachial-cephalic fistula
7A60200	attention to arteriovenous shunt
7A60300	removal of infected arteriovenous shunt
7A60400	banding of arteriovenous fistula
7A60500	thrombectomy of arteriovenous fistula
7A60600	creation of graft fistula for dialysis
7A60y00	other specified arteriovenous shunt
7A60z00	arteriovenous shunt nos
7A61100	repair of acquired arteriovenous fistula
7A61111	ligation of acquired arteriovenous fistula
7A61400	ligation of acquired arteriovenous fistula
7A61900	ligation of arteriovenous dialysis fistula
7A61A00	ligation of arteriovenous dialysis graft
7L1A000	renal dialysis
7L1Ay00	other specified compensation for renal failure
7L1Az00	compensation for renal failure nos
7L1B.00	placement ambulatory apparatus compensation renal failure
7L1B.11	placement ambulatory dialysis apparatus - compens renal fail
7L1B000	insertion of ambulatory peritoneal dialysis catheter
7L1B100	removal of ambulatory peritoneal dialysis catheter
7L1B200	flushing of peritoneal dialysis catheter
7L1By00	placement ambulatory apparatus- compensate renal failure os
7L1C.00	placement other apparatus for compensation for renal failure
7L1C000	insertion of temporary peritoneal dialysis catheter
7L1Cy00	placement other apparatus- compensate for renal failure os
7L1Cz00	placement other apparatus- compensate for renal failure nos
G72C.00	ruptured aneurysm of dialysis vascular access
G72D.00	aneurysm of dialysis arteriovenous fistula
G72D100	aneurysm of needle site of dialysis arteriovenous fistula
G72D200	aneurysm of anastomotic site of dialysis av fistula
G760.00	acquired arteriovenous fistula
Gy1..00	stenosis of dialysis vascular access
Gy21.00	thrombosis of dialysis arteriovenous fistula
Gy3..00	occlusion of dialysis vascular access
Gy31.00	occlusion of dialysis arteriovenous fistula
Gy40.00	infection of dialysis arteriovenous graft
Gy41.00	infection of dialysis arteriovenous fistula
Gy51.00	haemorrhage of dialysis arteriovenous fistula
Gy60.00	rupture of dialysis arteriovenous graft
SP01500	mechanical complication of dialysis catheter
SP01700	mechanical complication of arterio-venous surgical fistula
SP05613	[x] peritoneal dialysis associated peritonitis
SP06B00	continuous ambulatory peritoneal dialysis associated perit
SP07G00	stenosis of arteriovenous dialysis fistula

ReadCode	Rubric
SP07N00	arteriovenous fistula thrombosis
SP0G.00	anaphylactoid reaction due to haemodialysis
TA02000	accid cut;puncture;perf;h'ge - kidney dialysis
TA22.00	failure of sterile precautions during perfusion
TA22000	failure of sterile precautions during kidney dialysis
TB11.00	kidney dialysis with complication; without blame
TB11.11	renal dialysis with complication; without blame
U612200	[x]failure sterile precautions dur kidney dialys/other perf
Z1A..00	dialysis training
Z1A1.00	peritoneal dialysis training
Z1A2.00	haemodialysis training
Z919.00	care of haemodialysis equipment
Z919100	priming haemodialysis lines
Z919300	reversing haemodialysis lines
Z91A.00	peritoneal dialysis bag procedure
ZV56.00	[v]aftercare involving intermittent dialysis
ZV56000	[v]aftercare involving extracorporeal dialysis
ZV56011	[v]aftercare involving renal dialysis nos
ZV56100	[v]preparatory care for dialysis
ZV56y00	[v]other specified aftercare involving intermittent dialysis
ZV56y11	[v]aftercare involving peritoneal dialysis

Diastolic Blood Pressure:

ReadCode	Rubric
246A	O/E - Diastolic BP reading
246A.	O/E - Diastolic BP reading
246A.00	O/E - Diastolic BP reading
246a.00	Average night interval diastolic blood pressure
246P.00	Standing diastolic blood pressure
246R.00	Sitting diastolic blood pressure
246c.00	Average home diastolic blood pressure
246f.00	Ambulatory diastolic blood pressure
246V.00	Average 24 hour diastolic blood pressure
246X.00	Average day interval diastolic blood pressure
246V.	Average 24 hour diastolic blood pressure
246c.	Average home diastolic blood pressure
246f.	Ambulatory diastolic blood pressure
246R.	Sitting diastolic blood pressure

Haemoglobin:

ReadCode	Rubric
423	Haemoglobin estimation
423..	Haemoglobin estimation
423	Haemoglobin estimation
423..00	Haemoglobin estimation
423..11	Hb estimation
423Z.00	Haemoglobin estimation NOS
423Z.	Haemoglobin estimation NOS

Heart Rate:

ReadCode	Rubric
24c..00	Heart rate
24c..	Heart rate
242	O/E - pulse rate
242..	O/E - pulse rate
242..00	O/E - pulse rate
24c	Heart rate
242%	O/E - pulse rate

Ischaemic heart disease:

ReadCode	Rubric
14AL.00	H/O: Treatment for ischaemic heart disease
8H2V.00	Admit ischaemic heart disease emergency
G3	Ischaemic heart disease
G3...	Ischaemic heart disease
G3...00	Ischaemic heart disease
G3...13	IHD - Ischaemic heart disease
G30..00	Acute myocardial infarction
G30..11	Attack - heart
G30..12	Coronary thrombosis
G30..13	Cardiac rupture following myocardial infarction (MI)
G30..14	Heart attack
G30..15	MI - acute myocardial infarction
G30..16	Thrombosis - coronary
G30..17	Silent myocardial infarction
G300.00	Acute anterolateral infarction
G301.00	Other specified anterior myocardial infarction
G301000	Acute anteroapical infarction
G301100	Acute anteroseptal infarction
G301z00	Anterior myocardial infarction NOS
G302.00	Acute inferolateral infarction

ReadCode	Rubric
G303.00	Acute inferoposterior infarction
G304.00	Posterior myocardial infarction NOS
G305.00	Lateral myocardial infarction NOS
G306.00	True posterior myocardial infarction
G307.00	Acute subendocardial infarction
G307000	Acute non-Q wave infarction
G307100	Acute non-ST segment elevation myocardial infarction
G308.00	Inferior myocardial infarction NOS
G309.00	Acute Q-wave infarct
G30B.00	Acute posterolateral myocardial infarction
G30X.00	Acute transmural myocardial infarction of unspecif site
G30X000	Acute ST segment elevation myocardial infarction
G30y.00	Other acute myocardial infarction
G30y000	Acute atrial infarction
G30y100	Acute papillary muscle infarction
G30y200	Acute septal infarction
G30yz00	Other acute myocardial infarction NOS
G30z.00	Acute myocardial infarction NOS
G31..00	Other acute and subacute ischaemic heart disease
G310.00	Postmyocardial infarction syndrome
G311.13	Unstable angina
G311.14	Angina at rest
G311000	Myocardial infarction aborted
G311011	MI - myocardial infarction aborted
G311100	Unstable angina
G311200	Angina at rest
G311500	Acute coronary syndrome
G312.00	Coronary thrombosis not resulting in myocardial infarction
G31y.00	Other acute and subacute ischaemic heart disease
G31y000	Acute coronary insufficiency
G31y100	Microinfarction of heart
G31y200	Subendocardial ischaemia
G31y300	Transient myocardial ischaemia
G31yz00	Other acute and subacute ischaemic heart disease NOS
G32..00	Old myocardial infarction
G32..11	Healed myocardial infarction
G32..12	Personal history of myocardial infarction
G33z500	Post infarct angina
G34..00	Other chronic ischaemic heart disease
G340.11	Triple vessel disease of the heart
G344.00	Silent myocardial ischaemia
G34y.00	Other specified chronic ischaemic heart disease
G34yz00	Other specified chronic ischaemic heart disease NOS
G34z.00	Other chronic ischaemic heart disease NOS
G35..00	Subsequent myocardial infarction

ReadCode	Rubric
G350.00	Subsequent myocardial infarction of anterior wall
G351.00	Subsequent myocardial infarction of inferior wall
G353.00	Subsequent myocardial infarction of other sites
G35X.00	Subsequent myocardial infarction of unspecified site
G36..00	Certain current complication follow acute myocardial infarct
G360.00	Haemopericardium/current comp folow acut myocard infarct
G361.00	Atrial septal defect/curr comp folow acut myocardal infarct
G362.00	Ventric septal defect/curr comp fol acut myocardal infarctn
G363.00	Ruptur cardiac wall w'out haemopericard/cur comp fol ac MI
G364.00	Ruptur chordae tendinae/curr comp fol acute myocard infarct
G365.00	Rupture papillary muscle/curr comp fol acute myocard infarct
G38..00	Postoperative myocardial infarction
G380.00	Postoperative transmural myocardial infarction anterior wall
G381.00	Postoperative transmural myocardial infarction inferior wall
G384.00	Postoperative subendocardial myocardial infarction
G38z.00	Postoperative myocardial infarction; unspecified
G3z..00	Ischaemic heart disease NOS
Gyu3	[X]Ischaemic heart diseases
Gyu3.	[X]Ischaemic heart diseases
Gyu3.00	[X]Ischaemic heart diseases
Gyu3200	[X]Other forms of acute ischaemic heart disease
Gyu3300	[X]Other forms of chronic ischaemic heart disease
Gyu3400	[X]Acute transmural myocardial infarction of unspecif site
Gyu3600	[X]Subsequent myocardial infarction of unspecified site

Mean corpuscular volume:

ReadCode	Rubric
42A..	Mean corpuscular volume (MCV)
42A	Mean corpuscular volume (MCV)
42A..00	Mean corpuscular volume (MCV)

Mortality:

ReadCode	Rubric
22J..	Death
8HG..	Death in hospital
9495	Patient died in hospital
8HG..	Died in hospital
9493	Patient died in nursing home

ReadCode	Rubric
9491	Patient died at home
22J..	Died
22J..	Patient died
949B.	Patient died in community hospital
949D.	Patient died in care home
94B..	Cause of death
949A.	Patient died in hospice
22J..	O/E - dead
941..	Death certificate form Med A
9451	Death notif. from hospital
948..	Cremation certification
943..	Report for Coroner
94A..	Referral to coroner
R21..	[D]Sudden death, cause unknown
9485	Cremation form 4 completed
94E..	Date of death
949..	Died - place patient died
949..	Dead - place patient died
94A..	Unexpected death-Coroner told
22J2.	O/E - dead - expected
9412	Death cert. Med A signed
9494	Patient died in resid.inst.NOS
9481	Patient for cremation
9491	DEATH
949..	Deceased - place patient died
94F..	Unexpected death
945Z.	Hospital death disch. NOS
4K9..	Post mortem exam.
R213100	[D]Found dead
22J8.	Death - cause unknown
943Z.	Report for Coroner NOS

Nephrectomy:

ReadCode	Rubric
7B01	Total nephrectomy
7B01.	Total nephrectomy
7B01.00	Total nephrectomy
7B01.11	Total excision of kidney
7B010	Radical nephrectomy
7B01000	Radical nephrectomy
7B01011	Nephrectomy and excision of perirenal tissue
7B011	Nephroureterectomy-unspecified

ReadCode	Rubric
7B01100	Nephroureterectomy-unspecified
7B012	Bilateral nephrectomy
7B01200	Bilateral nephrectomy
7B013	Heminephrect- horseshoe kidney
7B01300	Heminephrectomy for horseshoe kidney
7B01311	Excision of half of horseshoe kidney
7B014	Simple nephrectomy - other
7B01400	Simple nephrectomy - other
7B015	Transplant nephrectomy
7B01500	Transplant nephrectomy
7B01511	Excision of rejected transplanted kidney
7B016	Simple nephrectomy -live donor
7B01600	Simple nephrectomy -live donor
7B017	Nephroureterec-open lower uret
7B01700	Nephroureterectomy with open lower ureterectomy
7B018	Nephrouretrec-pluck lower uret
7B01800	Nephroureterectomy with pluck lower ureterectomy
7B019	Excision of rejected Tx kidney
7B01y	Total nephrectomy OS
7B01y00	Other specified total nephrectomy
7B01z	Total nephrectomy NOS
7B01z00	Total nephrectomy NOS
7B02	Partial nephrectomy
7B02.	Partial nephrectomy
7B02.00	Partial nephrectomy
7B02.11	Partial excision of kidney
7B020	Heminephrectomy duplex kidney
7B02000	Heminephrectomy for duplex kidney
7B021	Division isthmus horseshoe kid
7B02100	Division of isthmus of horseshoe kidney
7B022	Upper pole partial nephrectomy
7B02200	Upper pole partial nephrectomy
7B023	Lower pole partial nephrectomy
7B02300	Lower pole partial nephrectomy
7B02y	Partial nephrectomy OS
7B02y00	Other specified partial nephrectomy
7B02z	Partial nephrectomy NOS
7B02z00	Partial nephrectomy NOS

Peripheral vascular disease:

ReadCode	Rubric
G73	Other peripheral vascular disease
G73..	Other peripheral vascular disease
G73..00	Other peripheral vascular disease
G73..11	Peripheral ischaemic vascular disease
G73..12	Ischaemia of legs
G73..13	Peripheral ischaemia
G73.	Other peripheral vascular disease

Renal Malignancy:

ReadCode	Rubric
B4A	Renal malignant neoplasm
B4A..	Malig neop kid/oth urinary org
B4A..00	Malig neop of kidney and other unspecified urinary organs
B4A..11	Renal malignant neoplasm
B4A0.	Malig neop kidney parenchyma
B4A0.00	Malignant neoplasm of kidney parenchyma
B4A00	Hypernephroma
B4A0000	Hypernephroma
B4A1.	Malig neop renal pelvis
B4A1.00	Malignant neoplasm of renal pelvis
B4A10	Malig neop renal calyces
B4A1000	Malignant neoplasm of renal calyces
B4A1100	Malignant neoplasm of ureteropelvic junction
B4A1z	Malig neop renal pelvis NOS
B4A1z00	Malignant neoplasm of renal pelvis NOS
B91z1	Renal neoplasm of uncertain behaviour
B91z100	Neoplasm of uncertain behaviour of kidney
B91z111	Renal neoplasm of uncertain behaviour
B91z3	Neoplasm of uncertain or unknown behaviour of renal pelvis
B91z300	Neoplasm of uncertain or unknown behaviour of renal pelvis
BB5a	[M]Renal adenoma and carcinoma
BB5a.	[M]Renal adenoma and carcinoma
BB5a.00	[M]Renal adenoma and carcinoma
BB5a000	[M]Renal cell carcinoma
BB5a012	[M]Hypernephroma
BB5az	[M]Renal adenoma/ca NOS
BB5az00	[M]Renal adenoma or carcinoma NOS
BBL7	[M]Mixed and stromal renal neoplasms
BBL7.00	[M]Mixed and stromal renal neoplasms

ReadCode	Rubric
BBL7.11	[M]Nephromas and nephroblastomas
BBL7000	[M]Mesoblastic nephroma
BBL7100	[M]Nephroblastoma NOS
BBL7111	[M]Adenosarcoma
BBL7112	[M]Wilms' tumour
BBL7200	[M]Epithelial nephroblastoma
BBL7300	[M]Mesenchymal nephroblastoma
ZV105	[V]Personal history of malignant neoplasm of kidney
BBL7.	[M]Renal mixed/stromal neoplas
BBL70	[M]Mesoblastic nephroma
BBL71	[M]Nephroblastoma NOS
BBL72	[M]Epithelial nephroblastoma
BBL73	[M]Mesenchymal nephroblastoma
BBL7z	[M]Renal mixed/strom. neop NOS

Renal Transplant:

ReadCode	Rubric
SP08H00	Acute rejection of renal transplant
SP08E00	Acute rejection of renal transplant - grade I
SP08F00	Acute rejection of renal transplant - grade II
SP08G00	Acute rejection of renal transplant - grade III
SP08D00	Acute-on-chronic rejection of renal transplant
7B00400	Allotransplantation kidney from cadaver, heart non-beating
7B00211	Allotransplantation of kidney from cadaver
7B00500	Allotransplantation of kidney from cadaver NEC
7B00300	Allotransplantation of kidney from cadaver, heart-beating
7B00111	Allotransplantation of kidney from live donor
7B00000	Autotransplant of kidney
7B00212	Cadaveric renal transplant
SP08J00	Chronic rejection of renal transplant
TB00100	Kidney transplant with complication, without blame
7B00y00	Other specified transplantation of kidney
SP08R00	Renal transplant rejection
TB00111	Renal transplant with complication, without blame
SP08P00	Stenosis of vein of transplanted kidney
7B00.00	Transplantation of kidney
7B00200	Transplantation of kidney from cadaver
7B00100	Transplantation of kidney from live donor
7B00z00	Transplantation of kidney NOS
SP08N00	Unexplained episode of renal transplant dysfunction
SP08T00	Urological complication of renal transplant
SP08W00	Vascular complication of renal transplant

ReadCode	Rubric
SP08V00	Very mild acute rejection of renal transplant
7B00600	Xenograft renal transplant
7B000	Autotransplant of kidney
7B001	Live donor kidney transplant
7B002	Cadaver donor kidney transplnt
7B003	Allotra kidney cad, heart-beat
7B004	Allot kid cad, heart non-beat
7B005	Allotranspl kidney cadaver NEC
7B006	Xenograft renal transplant
7B00y	Transplantation of kidney OS
7B00z	Transplantation of kidney NOS
SP083	Kidney transplant fail+rejectn
SP08a	Thromb vein transplantd kidney
SP08b	De novo glomerulonephritis
SP08C	Accel reject renal transplant
SP08D	Acute-on-chr rejec ren transp
SP08E	Acut reject renal trans grad I
SP08F	Acu reject renal trans grad II
SP08G	Acu reject rena trans grad III
SP08H	Acute reject renal transplant
SP08J	Chr rejection, renal transp
SP08K	Chr rejec, renal transp-gde 1
SP08L	Chr rejec, renal transp-gde II
SP08M	Chr rejec, ren transp-gde III
SP08N	Unexplaind renal trans dysfunc
SP08P	Stenos vein transplantd kidney
SP08Q	Aneurysm arty transplntd kdny
SP08R	Renal transplant rejection
SP08S	Aneurysm vein transplantd kdny
SP08T	Urological complicatn renal Tx
SP08V	V mild acute rejec, ren transp
SP08W	Vasc complictn renal transplnt
SP08X	Rupt artry transplanted kidney
SP08Y	Ruptu vein transplanted kidney
SP08Z	Thromb artery trnsplntd kidney
TB001	Kidney transplant+complication

Serum Albumin:

ReadCode	Rubric
44M4.	Serum albumin
44M4	Serum albumin
44MI.	Plasma albumin level
44MI	Plasma albumin level
44M4.00	Serum albumin

Serum Potassium:

ReadCode	Rubric
44I4.00	Serum potassium
44I4.	Serum potassium

Serum Sodium:

ReadCode	Rubric
44I5.00	Serum sodium
44I5.	Serum sodium

Smoking:

ReadCode	Smoking	Rubric
137Y.00	1	Cigar consumption
137J.	1	Cigar smoker
137J	1	Cigar smoker
137J.00	1	Cigar smoker
137X.	1	Cigarette consumption
137X	1	Cigarette consumption
137X.00	1	Cigarette consumption
137P.	1	Cigarette smoker
137P	1	Cigarette smoker
137P.00	1	Cigarette smoker
137L.	0	Current non-smoker
137L	0	Current non-smoker
137L.00	0	Current non-smoker
137R. 00	1	Current smoker
137R	1	Current smoker
137R.00	1	Current smoker

ReadCode	Smoking	Rubric
137T.	0	Date ceased smoking
137T	0	Date ceased smoking
137T.00	0	Date ceased smoking
137O.	0	Ex cigar smoker
137O	0	Ex cigar smoker
137O.00	0	Ex cigar smoker
137N.	0	Ex pipe smoker
137N	0	Ex pipe smoker
137N.00	0	Ex pipe smoker
137l.	0	Ex roll-up cigarette smoker
137l	0	Ex roll-up cigarette smoker
137l.00	0	Ex roll-up cigarette smoker
137S.	0	Ex smoker
137S	0	Ex smoker
137S.00	0	Ex smoker
137j	0	Ex-cigarette smoker
137j.00	0	Ex-cigarette smoker
137A.	0	Ex-heavy smoker (20-39/day)
137A	0	Ex-heavy smoker (20-39/day)
137A.00	0	Ex-heavy smoker (20-39/day)
1378	0	Ex-light smoker (1-9/day)
1378	0	Ex-light smoker (1-9/day)
1379	0	Ex-moderate smoker (10-19/day)
1379	0	Ex-moderate smoker (10-19/day)
137F.	0	Ex-smoker - amount unknown
137F	0	Ex-smoker - amount unknown
137F.00	0	Ex-smoker - amount unknown
1377	0	Ex-trivial smoker (<1/day)
1377	0	Ex-trivial smoker (<1/day)
137B.	0	Ex-very heavy smoker (40+/day)
137B	0	Ex-very heavy smoker (40+/day)
137B.00	0	Ex-very heavy smoker (40+/day)
137m.00	1	Failed attempt to stop smoking
1375	1	Heavy smoker - 20-39 cigs/day
1375	1	Heavy smoker - 20-39 cigs/day
137C.	1	Keeps trying to stop smoking
137C	1	Keeps trying to stop smoking
137C.00	1	Keeps trying to stop smoking
1373	1	Light smoker - 1-9 cigs/day
1373	1	Light smoker - 1-9 cigs/day
137h.00	1	Minutes from waking to first tobacco consumption
1374	1	Moderate smoker - 10-19 cigs/d
1374	1	Moderate smoker - 10-19 cigs/d
1371	0	Never smoked tobacco

ReadCode	Smoking	Rubric
1371	0	Never smoked tobacco
1371.11	0	Non-smoker
137U.00	0	Not a passive smoker
137d.00	1	Not interested in stopping smoking
1372.11	0	Occasional smoker
137H.	1	Pipe smoker
137H	1	Pipe smoker
137H.00	1	Pipe smoker
137a. 00	1	Pipe tobacco consumption
137a	1	Pipe tobacco consumption
137a.00	1	Pipe tobacco consumption
137b.00	1	Ready to stop smoking
137f.	1	Reason for restarting smoking
137f	1	Reason for restarting smoking
137f.00	1	Reason for restarting smoking
137K0	0	Recently stopped smoking
137K000	0	Recently stopped smoking
137M.	1	Rolls own cigarettes
137M	1	Rolls own cigarettes
137M.00	1	Rolls own cigarettes
137P.11	1	Smoker
137..11	1	Smoker - amount smoked
137V.	1	Smoking reduced
137V	1	Smoking reduced
137V.00	1	Smoking reduced
137e.	1	Smoking restarted
137e	1	Smoking restarted
137e.00	1	Smoking restarted
137Q.11	1	Smoking restarted
137Q.	1	Smoking started
137Q	1	Smoking started
137Q.00	1	Smoking started
137K.	0	Stopped smoking
137K	0	Stopped smoking
137K.00	0	Stopped smoking
137c.00	1	Thinking about stopping smoking
137Z.	1	Tobacco consumption NOS
137Z	1	Tobacco consumption NOS
137Z.00	1	Tobacco consumption NOS
137G.	1	Trying to give up smoking
137G	1	Trying to give up smoking
137G.00	1	Trying to give up smoking
1376	1	Very heavy smoker - 40+cigs/d
1376	1	Very heavy smoker - 40+cigs/d

Systolic Blood Pressure:

ReadCode	Rubric
2469	O/E - Systolic BP reading
246e.0	Ambulatory systolic blood pressure
246Q.00	Sitting systolic blood pressure
246W.00	Average 24 hour systolic blood pressure
246Y.00	Average day interval systolic blood pressure
246d.00	Average home systolic blood pressure
246b.00	Average night interval systolic blood pressure
246W.	Average 24 hour systolic blood pressure
246e.	Ambulatory systolic blood pressure
246N.	Standing systolic blood pressure
246d.	Average home systolic blood pressure
246Q.	Sitting systolic blood pressure

Uric Acid:

ReadCode	Rubric
44K..	Blood urate
44K	Blood urate
44K5.	Serum urate level
44K5	Serum urate level
44K6.	Plasma urate level
44K6	Plasma urate level
44KZ.	Blood urate NOS
44KZ	Blood urate NOS
44K..11	Serum uric acid
44K5.00	Serum urate level
44K6.00	Plasma urate level
44K..00	Blood urate
44KZ.00	Blood urate NOS

Urine Albumin:

ReadCode	Rubric
46N4.	Urine albumin
46N4	Urine albumin
46N4.00	Urine albumin

Urine Albimin:Creatinine Ratio:

ReadCode	Rubric
46TC.00	Urine albumin:creatinine ratio
44J7.	Albumin / creatinine ratio
46TC.	Urine albumin:creatinine ratio
46TD.	Urine microalbumin:creatinine ratio
44J7	Albumin / creatinine ratio
46TC	Urine albumin:creatinine ratio
46TD	Urine microalbumin:creatinine ratio
44J7.00	Albumin / creatinine ratio
46TC.00	Urine albumin:creatinine ratio
46TD.00	Urine microalbumin:creatinine ratio

Angiotensin converting enzyme inhibitors:

ReadCode	Rubric
bi...	ANGIOTENSIN-CONVERTING ENZYME INHIBITORS
bi1..	CAPTOPRIL
bi11.	ACEPRIL 12.5mg tablets
bi12.	ACEPRIL 25mg tablets
bi13.	ACEPRIL 25mg tablets x56
bi14.	ACEPRIL 50mg tablets
bi15.	ACEPRIL 50mg tablets x56
bi16.	*CAPOTEN 12.5mg tablets
bi17.	CAPOTEN 25mg tablets
bi18.	CAPOTEN 25mg tablets x56
bi19.	CAPOTEN 50mg tablets
bi1A.	*HYPAPRIL 12.5mg tablets
bi1B.	*HYPAPRIL 25mg tablets
bi1C.	*HYPAPRIL 50mg tablets
bi1D.	*CAPTO-CO 25mg/12.5mg tablets
bi1E.	*CAPTO-CO 50mg/25mg tablets
bi1F.	CO-ZIDOCAPT 25mg/12.5mg tablet
bi1G.	*CO-ZIDOCAPT 50mg/25mg tablets
bi1H.	NOYADA 5mg/5mL oral solution
bi1I.	CAPTOPRIL 5mg/5mL oral solution
bi1J.	NOYADA 25mg/5mL oral solution
bi1K.	CAPTOPRIL 25mg/5mL oral solution
bi1a.	CAPOTEN 50mg tablets x56
bi1b.	ACEZIDE 50mg tablets x56
bi1c.	*CAPOZIDE 50mg tablets x28
bi1d.	*CAPOZIDE LS 25mg tabletsx28CP
bi1g.	ECOPACE 12.5mg tablets
bi1h.	ECOPACE 25mg tablets

ReadCode	Rubric
bi1i.	ECOPACE 50mg tablets
bi1k.	*KAPLON 25mg tablets
bi1l.	*KAPLON 50mg tablets
bi1m.	*HYTENEZE 12.5 tablets
bi1n.	*HYTENEZE 25 tablets
bi1o.	*HYTENEZE 50 tablets
bi1p.	*TENSOPRIL 12.5mg tablets
bi1q.	*TENSOPRIL 25mg tablets
bi1r.	*TENSOPRIL 50mg tablets
bi1s.	CAPOZIDE 50mg/25mg tablets
bi1v.	CAPTOPRIL 12.5mg tablets
bi1w.	CAPTOPRIL 25mg tablets
bi1x.	CAPTOPRIL 25mg tablets x56
bi1y.	CAPTOPRIL 50mg tablets x56
bi1z.	CAPTOPRIL 50mg tablets
bi2..	ENALAPRIL MALEATE
bi21.	INNOVACE 2.5mg tablets
bi22.	INNOVACE 5mg tablets
bi23.	INNOVACE 5mg tablets x28
bi24.	INNOVACE 10mg tablets
bi25.	INNOVACE 10mg tablets x28
bi26.	INNOVACE 20mg tablets
bi27.	INNOVACE 20mg tablets x28
bi28.	INNOZIDE 20/12.5mg tablets
bi29.	INNOVACE tablets titration pack
bi2A.	*ENALAPRIL MALEATE 2.5mg wafer
bi2B.	*ENALAPRIL MALEATE 5mg wafer
bi2C.	*ENALAPRIL MALEATE 10mg wafer
bi2D.	*ENALAPRIL MALEATE 20mg wafer
bi2E.	*INNOVACE MELT 2.5mg wafer
bi2F.	*INNOVACE MELT 5mg wafer
bi2G.	*INNOVACE MELT 10mg wafer
bi2H.	*INNOVACE MELT 20mg wafer
bi2J.	*PRALENAL 2.5mg tablets
bi2K.	*PRALENAL 5mg tablets
bi2L.	*PRALENAL 10mg tablets
bi2M.	*PRALENAL 20mg tablets
bi2a.	ENALAPRIL MALEATE tablets titration pack
bi2t.	ENALAPRIL MALEATE 2.5mg tablets
bi2u.	ENALAPRIL MALEATE 5mg tablets
bi2v.	ENALAPRIL MALEATE 5mg tablets x28
bi2w.	ENALAPRIL MALEATE 10mg tablets
bi2x.	ENALAPRIL MALEATE 10mg tablets x28
bi2y.	ENALAPRIL MALEATE 20mg tablets
bi2z.	ENALAPRIL MALEATE 20mg tablets x28

ReadCode	Rubric
bi3..	LISINOPRIL
bi31.	LISINOPRIL 2.5mg tablets
bi32.	LISINOPRIL 5mg tablets
bi33.	LISINOPRIL 10mg tablets
bi34.	LISINOPRIL 20mg tablets
bi35.	*CARACE 2.5mg tablets
bi36.	*CARACE 5mg tablets 28CP
bi37.	*CARACE 5mg tablets
bi38.	*CARACE 10mg tablets 28CP
bi39.	*CARACE 10mg tablets
bi3a.	*CARACE 20mg tablets 28CP
bi3b.	*CARACE 20mg tablets
bi3c.	*ZESTRIL 2.5mg tablets 28CP
bi3d.	*ZESTRIL 2.5mg tablets
bi3e.	ZESTRIL 5mg tablets 28CP
bi3f.	ZESTRIL 5mg tablets
bi3g.	ZESTRIL 10mg tablets 28CP
bi3h.	ZESTRIL 10mg tablets
bi3i.	ZESTRIL 20mg tablets 28CP
bi3j.	ZESTRIL 20mg tablets
bi3k.	CARACE 20 PLUS tablets
bi3l.	*CARACE 10 PLUS tablets
bi3m.	*ZESTORETIC tablets 28CP
bi3n.	ZESTORETIC 20/12.5mg tablets
bi3q.	*ZESTRIL 2.5mg starter pack
bi3r.	LISINOPRIL 2.5mg tablets starter pack
bi3s.	ZESTORETIC 10/12.5mg tablets
bi3u.	*CARALPHA 10/12.5mg tablets
bi3v.	*CARALPHA 20/12.5mg tablets
bi3w.	LISICOSTAD HCT 20/12.5mg tablets
bi3x.	LISICOSTAD HCT 10/12.5mg tablets
bi3y.	LISINOPRIL 1mg/mL oral solution
bi4..	QUINAPRIL
bi41.	QUINAPRIL 5mg tablets
bi42.	QUINAPRIL 10mg tablets
bi43.	QUINAPRIL 20mg tablets
bi44.	ACCUPRO 5mg tablets 28CP
bi45.	ACCUPRO 10mg tablets 28CP
bi46.	ACCUPRO 20mg tablets 28CP
bi47.	ACCURETIC tablets
bi49.	ACCUPRO 40mg tablets
bi4A.	QUINAPRIL 40mg tablets
bi4B.	QUINIL 5mg tablets
bi4C.	QUINIL 10mg tablets
bi4D.	QUINIL 20mg tablets

ReadCode	Rubric
bi4E.	QUINIL 40mg tablets
bi5..	PERINDOPRIL ERBUMINE
bi51.	PERINDOPRIL ERBUMINE 2mg tablets
bi52.	PERINDOPRIL ERBUMINE 4mg tablets
bi53.	*COVERSYL 2mg tablets
bi54.	*COVERSYL 4mg tablets
bi56.	COVERSYL PLUS 4mg/1.25mg tablets
bi57.	PERINDOPRIL ERBUMINE 8mg tablets
bi58.	*COVERSYL 8mg tablets
bi6..	RAMIPRIL
bi61.	RAMIPRIL 1.25mg capsules
bi62.	RAMIPRIL 2.5mg capsules
bi63.	RAMIPRIL 5mg capsules
bi64.	*TRITACE 1.25mg capsules
bi65.	*TRITACE 2.5mg capsules
bi66.	*TRITACE 5mg capsules
bi67.	RAMIPRIL 10mg capsules
bi68.	*TRITACE 10mg capsules
bi6A.	TRITACE Titration Pack capsules
bi6B.	RAMIPRIL 1.25mg tablets
bi6C.	RAMIPRIL 2.5mg tablets
bi6D.	RAMIPRIL 5mg tablets
bi6E.	RAMIPRIL 10mg tablets
bi6F.	RAMIPRIL 2.5mg+5mg+10mg tablets titration pack
bi6G.	RAMIPRIL 2.5mg/5mL oral solution
bi6o.	TRITACE Titration Pack tablets
bi6p.	*RANACE 10mg capsules
bi6q.	*RANACE 5mg capsules
bi6r.	*RANACE 2.5mg capsules
bi6s.	*RANACE 1.25mg capsules
bi6t.	*LOPACE 2.5mg capsules
bi6u.	*LOPACE 5mg capsules
bi6v.	*LOPACE 10mg capsules
bi6w.	TRITACE 10mg tablets
bi6x.	TRITACE 5mg tablets
bi6y.	TRITACE 2.5mg tablets
bi6z.	TRITACE 1.25mg tablets
bi7..	SODIUM FOSINOPRIL
bi71.	FOSINOPRIL 10mg tablets
bi72.	FOSINOPRIL 20mg tablets
bi73.	*STARIL 10mg tablets
bi74.	*STARIL 20mg tablets
bi8..	CILAZAPRIL
bi81.	CILAZAPRIL 250micrograms tablets
bi82.	CILAZAPRIL 500micrograms tablets

ReadCode	Rubric
bi83.	*CILAZAPRIL 1mg tablets
bi84.	*CILAZAPRIL 2.5mg tablets
bi85.	*VASCACE 250micrograms tablets
bi86.	*VASCACE 500micrograms tablets
bi87.	*VASCACE 1mg tablets
bi88.	*VASCACE 2.5mg tablets
bi89.	*VASCACE 5mg tablets
bi8a.	CILAZAPRIL 5mg tablets
bi9..	TRANDOLAPRIL
bi91.	TRANDOLAPRIL 500micrograms capsules
bi91.	TRANDOLAPRIL 500micrograms capsules
bi92.	TRANDOLAPRIL 1mg capsules
bi93.	TRANDOLAPRIL 2mg capsules
bi94.	*GOPTEN 500micrograms capsules
bi95.	*GOPTEN 1mg capsules
bi96.	*GOPTEN 2mg capsules
bi97.	*ODRIK 500micrograms capsules
bi98.	*ODRIK 1mg capsules
bi99.	*ODRIK 2mg capsules
bi9A.	*GOPTEN 4mg capsules
bi9z.	TRANDOLAPRIL 4mg capsules
biA..	MOEXIPRIL
biA1.	MOEXIPRIL HYDROCHLORIDE 7.5mg tablets
biA2.	MOEXIPRIL HYDROCHLORIDE 15mg tablets
biA3.	PERDIX 7.5mg tablets
biA4.	PERDIX 15mg tablets
biB..	IMIDAPRIL HYDROCHLORIDE
biB1.	TANATRIL 5mg tablets
biB2.	TANATRIL 10mg tablets
biB3.	TANATRIL 20mg tablets
biBx.	IMIDAPRIL HYDROCHLORIDE 20mg tablets
biBy.	IMIDAPRIL HYDROCHLORIDE 5mg tablets
biBz.	IMIDAPRIL HYDROCHLORIDE 10mg tablets
biC..	PERINDOPRIL ARGININE
biC1.	COVERSYL ARGININE 2.5mg tablets
biC2.	PERINDOPRIL ARGININE 2.5mg tablets
biC3.	COVERSYL ARGININE 5mg tablets
biC4.	PERINDOPRIL ARGININE 5mg tablets
biC5.	COVERSYL ARGININE 10mg tablets
biC6.	PERINDOPRIL ARGININE 10mg tablets
biC7.	COVERSYL ARGININE PLUS 5mg/1.25mg tablets

Aldosterone antagonists:

ReadCode	Rubric
b4...	POTASSIUM SPARING DIURETICS
b41..	AMILORIDE HYDROCHLORIDE
b411.	*MIDAMOR 5mg tablets
b412.	*AMILOSPARE 5mg tablets
b413.	AMILORIDE 5mg/5mL sugar free solution
b414.	*BERKAMIL 5mg tablets
b415.	AMILAMONT 5mg/5mL sugar free oral solution
b41z.	AMILORIDE HCL 5mg tablets
b42..	POTASSIUM CANRENOATE
b421.	SPIROCTAN-M 200mg/10mL injection
b42z.	POTASSIUM CANRENOATE 200mg/10mL injection
b43..	SPIRONOLACTONE
b431.	SPIRONOLACTONE 25mg tablets
b432.	SPIRONOLACTONE 50mg tablets
b433.	SPIRONOLACTONE 100mg tablets
b434.	ALDACTONE 25mg tablets
b435.	ALDACTONE 50mg tablets
b436.	ALDACTONE 100mg tablets
b437.	*DIATENSEC 50mg tablets
b438.	*LARACTONE 25mg tablets
b439.	*LARACTONE 100mg tablets
b43A.	*SPIROSPARE 25mg tablets
b43a.	SPIRETIC 25mg tablets
b43b.	SPIRETIC 100mg tablets
b43c.	*SPIROCTAN 25mg tablets
b43d.	*SPIROCTAN 50mg tablets
b43e.	*SPIROCTAN 100mg capsules
b43f.	*SPIROLONE 25mg tablets
b43g.	*SPIROLONE 50mg tablets
b43h.	*SPIROLONE 100mg tablets
b43i.	*LARACTONE 50mg tablets
b43k.	SPIRONOLACTONE 5mg/5mL oral suspension
b43l.	SPIRONOLACTONE 10mg/5mL oral suspension
b43m.	SPIRONOLACTONE 25mg/5mL oral suspension
b43n.	SPIRONOLACTONE 50mg/5mL oral suspension
b43z.	*SPIRONOLACTONE 100mg capsules
b44..	TRIAMTERENE
b441.	DYTAC 50mg capsules
b44z.	TRIAMTERENE 50mg capsules
b45..	EPLERENONE
b451.	INSPRA 25mg tablets
b452.	INSPRA 50mg tablets
b45y.	EPLERENONE 50mg tablets

ReadCode	Rubric
b45z.	EPLERENONE 25mg tablets
b5...	POTASSIUM SPARING COMPOUND DIURETICS
b51..	POTASSIUM SPARING COMPOUND DIURETICS A-Z
b511.	ALDACTIDE-25 tablets
b512.	ALDACTIDE-50 tablets
b513.	*AMILCO tablets
b514.	DYAZIDE tablets
b515.	*DYTIDE capsules
b516.	FRUMIL 40/5mg tablets
b517.	FRUSENE tablets
b518.	KALSPARE tablets
b519.	LASILACTONE capsules
b51A.	CO-TRIAMTERZIDE 50/25mg tablets
b51B.	*FRU-CO 40/5mg tablets
b51C.	AMILORIDE HCL+CYCLOPENTHIAZIDE 2.5mg/250micrograms tablets
b51D.	AMILORIDE HCL+BUMETANIDE 5mg/1mg tablets
b51E.	TRIAMTERENE+BENZTHIAZIDE 50mg/25mg capsules
b51F.	TRIAMTERENE+CHLORTHALIDONE 50mg/25mg tablets
b51G.	TRIAMTERENE+CHLORTALIDONE 50mg/50mg tablets
b51H.	TRIAMTERENE+FUROSEMIDE 50mg/40mg tablets
b51J.	SPIRONOLACTONE+FUROSEMIDE 50mg/20mg capsules
b51K.	*DELVAS tablets
b51L.	*ARIDIL 2.5mg/20mg tablets
b51M.	*ARIDIL 5mg/40mg tablets
b51N.	*ARIDIL 10mg/80mg tablets
b51O.	*SPIRO-CO 25mg tablets
b51P.	*SPIRO-CO 50mg tablets
b51Q.	*ZIDA-CO 5mg/50mg tablets
b51R.	*FRUSEMEK 5mg/40mg tablets
b51S.	*FROOP CO 5mg/40mg tablets
b51T.	*KOMIL 5/40 tablets
b51a.	MODURET-25 tablets
b51b.	MODURETIC tablets
b51c.	*MODURETIC mixture
b51d.	*NORMETIC tablets
b51e.	*SYNURETIC tablets
b51f.	*TRIAMCO tablets
b51g.	*HYPERTANE-50 tablets
b51h.	*LASORIDE tablets
b51i.	*CO-AMILOFRUSE tablets
b51j.	CO-AMILOZIDE 2.5/25mg tablets
b51k.	CO-AMILOZIDE 5/50mg tablets
b51l.	CO-AMILOZIDE 5mg/50mg/5mL mixture
b51m.	VASETIC CO-AMILOZIDE 5/50mg tablets

ReadCode	Rubric
b51n.	*FRUSENE tablets 56CP
b51o.	FRUMIL LS 20/2.5mg tablets
b51p.	CO-FLUMACTONE-25 tablets
b51q.	CO-FLUMACTONE-50 tablets
b51r.	NAVISPARE 2.5/0.25mg tablets
b51s.	*AMILMAXCO 5/50 tablets
b51t.	*BURINEX A tablets
b51u.	*FRUMIL FORTE 80/10mg tablets
b51v.	*TRIAMAXCO 50/25mg tablets
b51w.	*KALSPARE LS tablets
b51x.	CO-AMILOFRUSE 2.5/20mg tablets
b51y.	CO-AMILOFRUSE 5/40mg tablets
b51z.	CO-AMILOFRUSE 10/80mg tablets

Angiotensin receptor blockers:

ReadCode	Rubric
bk...	OTHER ANTIHYPERTENSIVES
bk3..	LOSARTAN
bk31.	LOSARTAN POTASSIUM 25mg tablets
bk32.	LOSARTAN POTASSIUM 50mg tablets
bk33.	COZAAR HALF-STRENGTH 25mg tablets
bk34.	COZAAR 50mg tablets
bk35.	LOSARTAN POTASSIUM+HYDROCHLOROTHIAZIDE 50mg/12.5mg tablets
bk36.	COZAAR-COMP 50mg/12.5mg tablets
bk37.	LOSARTAN POTASSIUM 100mg tablets
bk38.	COZAAR 100mg tablets
bk39.	COZAAR-COMP 100mg/25mg tablets
bk3A.	COZAAR-COMP 100mg/12.5mg tablets
bk3B.	COZAAR 12.5mg tablets
bk3C.	LOSARTAN POTASSIUM 12.5mg tablets
bk3D.	COZAAR 2.5mg/mL oral suspension
bk3E.	LOSARTAN POTASSIUM 2.5mg/mL oral suspension
bk3F.	ZOVENCAL 25mg tablets
bk3G.	ZOVENCAL 50mg tablets
bk3H.	ZOVENCAL 100mg tablets
bk4..	VALSARTAN
bk41.	VALSARTAN 40mg capsules
bk42.	VALSARTAN 80mg capsules
bk43.	VALSARTAN 160mg capsules
bk44.	DIOVAN 40mg capsules
bk45.	DIOVAN 80mg capsules
bk46.	DIOVAN 160mg capsules

ReadCode	Rubric
bk47.	CO-DIOVAN 160mg/12.5mg tablets
bk48.	CO-DIOVAN 160mg/25mg tablets
bk49.	CO-DIOVAN 80mg/12.5mg tablets
bk4A.	DIOVAN 40mg tablets
bk4B.	DIOVAN 320mg tablets
bk4C.	DIOVAN 3mg/mL oral solution
bk4s.	VALSARTAN 80mg tablets
bk4t.	VALSARTAN 160mg tablets
bk4u.	VALSARTAN 3mg/mL oral solution
bk4v.	VALSARTAN 320mg tablets
bk4w.	VALSARTAN 40mg tablets
bk5..	IRBESARTAN
bk51.	IRBESARTAN 75mg tablets
bk52.	IRBESARTAN 150mg tablets
bk53.	IRBESARTAN 300mg tablets
bk54.	APROVEL 75mg tablets
bk55.	APROVEL 150mg tablets
bk56.	APROVEL 300mg tablets
bk57.	COAPROVEL 150mg/12.5mg tablets
bk58.	COAPROVEL 300mg/12.5mg tablets
bk59.	COAPROVEL 300mg/25mg tablets
bk6..	TRANDOLAPRIL+VERAPAMIL HYDROCHLORIDE
bk61.	TRANDOLAPRIL+VERAPAMIL HYDROCHLORIDE 2mg/180mg m/r capsules
bk62.	*TARKA 2mg/180mg m/r capsules
bk7..	CANDESARTAN CILEXETIL
bk71.	CANDESARTAN CILEXETIL 2mg tablets
bk72.	CANDESARTAN CILEXETIL 4mg tablets
bk73.	CANDESARTAN CILEXETIL 8mg tablets
bk74.	CANDESARTAN CILEXETIL 16mg tablets
bk75.	AMIAS 2mg tablets
bk76.	AMIAS 4mg tablets
bk77.	AMIAS 8mg tablets
bk78.	AMIAS 16mg tablets
bk79.	AMIAS 32mg tablets
bk7z.	CANDESARTAN CILEXETIL 32mg tablets
bk8..	TELMISARTAN
bk81.	TELMISARTAN 40mg tablets
bk82.	TELMISARTAN 80mg tablets
bk83.	MICARDIS 40mg tablets
bk84.	MICARDIS 80mg tablets
bk85.	MICARDIS 20mg tablets
bk86.	MICARDISPLUS 40mg/12.5mg tablets
bk87.	MICARDISPLUS 80mg/12.5mg tablets
bk88.	MICARDISPLUS 80mg/25mg tablets

ReadCode	Rubric
bk8z.	TELMISARTAN 20mg tablets
bk9..	EPROSARTAN
bk91.	TEVETEN 300mg tablets
bk92.	*TEVETEN 400mg tablets
bk93.	TEVETEN 600mg tablets
bk9x.	EPROSARTAN 300mg tablets
bk9y.	EPROSARTAN 400mg tablets
bk9z.	EPROSARTAN 600mg tablets
bkA..	BOSENTAN
bkA1.	BOSENTAN MONOHYDRATE 62.5mg tablets
bkA2.	BOSENTAN MONOHYDRATE 125mg tablets
bkA3.	TRACLEER 62.5mg tablets
bkA4.	TRACLEER 125mg tablets
bkB..	OLMESARTAN
bkB1.	OLMESARTAN MEDOXOMIL 10mg tablets
bkB2.	OLMESARTAN MEDOXOMIL 20mg tablets
bkB3.	OLMESARTAN MEDOXOMIL 40mg tablets
bkB4.	OLMETEC 10mg tablets
bkB5.	OLMETEC 20mg tablets
bkB6.	OLMETEC 40mg tablets
bkD..	AMLODIPINE + VALSARTAN
bkD1.	AMLODIPINE+VALSARTAN 5mg/80mg tablets
bkD2.	AMLODIPINE+VALSARTAN 5mg/160mg tablets
bkD3.	AMLODIPINE+VALSARTAN 10mg/160mg tablets
bkDx.	EXFORGE 10mg/160mg tablets
bkDy.	EXFORGE 5mg/160mg tablets
bkDz.	EXFORGE 5mg/80mg tablets
bkE1.	*THELIN 100mg tablets
bkEz.	SITAXENTAN SODIUM 100mg tablets
bkF..	ALISKIREN
bkF1.	RASILEZ 150mg tablets
bkF2.	RASILEZ 300mg tablets
bkFy.	ALISKIREN 300mg tablets
bkFz.	ALISKIREN 150mg tablets
bkG..	AMBRISENTAN
bkG1.	VOLIBRIS 5mg tablets
bkG2.	VOLIBRIS 10mg tablets
bkGy.	AMBRISENTAN 10mg tablets
bkGz.	AMBRISENTAN 5mg tablets
bkH..	OLMESARTAN+AMLODIPINE
bkH1.	SEVIKAR 20mg/5mg tablets
bkH2.	SEVIKAR 40mg/5mg tablets
bkH3.	SEVIKAR 40mg/10mg tablets
bkHx.	OLMESARTAN MEDOXOMIL+AMLODIPINE 40mg/10mg tablets

ReadCode	Rubric
bkHy.	OLMESARTAN MEDOXOMIL+AMLODIPINE 40mg/5mg tablets
bkHz.	OLMESARTAN MEDOXOMIL+AMLODIPINE 20mg/5mg tablets
bkJ..	AZILSARTAN
bkJ1.	EDARBI 20mg tablets
bkJ2.	AZILSARTAN MEDOXOMIL 20mg tablets
bkJ3.	EDARBI 40mg tablets
bkJ4.	AZILSARTAN MEDOXOMIL 40mg tablets
bkJ5.	EDARBI 80mg tablets
bkJ6.	AZILSARTAN MEDOXOMIL 80mg tablets
bkK..	MACITENTAN
bkK1.	OPSUMIT 10mg tablets
bkK2.	MACITENTAN 10mg tablets

Antimicrobials:

ReadCode	Rubric
e81..	GENTAMICIN [INFECTIONS]
eh1..	AMPHOTERICIN [ANTI FUNGAL]
ei1..	ACYCLOVIR [SYSTEMIC]
e82..	AMIKACIN
e87..	TOBRAMYCIN [SYSTEMIC]
e85..	NEOMYCIN SULFATE [SYSTEMIC]
ed1..	CAPREOMYCIN
eiI..	CIDOFOVIR
eg6..	CIPROFLOXACIN
ei8..	FOSCARNET
e6g..	IMIPENEM+CILASTATIN
e85..	NEOMYCIN SULFATE [SYSTEMIC]
ey1..	PENTAMIDINE ISETHIONATE
eb3..	COLISTIN
ed6..	RIFAMPICIN
ec...	SULFONAMIDES & TRIMETHOPRIM
e7...	TETRACYCLINES [SYSTEMIC]

Immunosuppressants:

ReadCode	Rubric
h82..	CICLOSPORIN
h83..	TACROLIMUS
h85..	SIROLIMUS
h34..	METHOTREXATE
h3G..	METHOTREXATE(2)

j52..	PENICILLAMINE [MUSCULOSKELETAL USE]
j56..	GOLD - AURANOFIN
hf...	INTERLEUKINS
h12..	CARMUSTINE
h53..	CISPLATIN
h17..	IFOSFAMIDE
h26..	PLICAMYCIN
hg1..	TRETINOIN [CYTOSTATIC]

Loop Diuretics:

ReadCode	Rubric
b3…	LOOP DIURETICS
b31..	FUROSEMIDE
b311.	FUROSEMIDE 20mg tablets
b312.	FUROSEMIDE 40mg tablets
b313.	FUROSEMIDE 500mg tablets
b314.	*ALUZINE 20mg tablets
b315.	*ALUZINE 40mg tablets
b316.	*ALUZINE 500mg tablets
b317.	*DIURESAL 40mg tablets
b318.	*DIURESAL 20mg/2mL injection
b319.	*DIURESAL 50mg/5mL injection
b31A.	MIN-I-JET FRUSEMIDE 250mg/25mL injection
b31B.	MIN-I-JET FRUSEMIDE 80mg/8mL injection
b31C.	FUROSEMIDE 80mg/8mL prefilled syringe
b31D.	FRUSEMIDE 250mg/25mL prefilled syringe
b31E.	FROOP 40mg tablets
b31F.	FRUSOL 20mg/5mL sugar free oral solution
b31G.	FRUSOL 40mg/5mL sugar free oral solution
b31H.	FRUSOL 50mg/5mL sugar free oral solution
b31a.	*DRYPTAL 40mg tablets
b31b.	*DRYPTAL 500mg tablets
b31c.	*DRYPTAL 20mg/2mL injection
b31d.	*DRYPTAL 50mg/5mL injection
b31e.	*DRYPTAL 250mg/25mL injection
b31f.	*FRUSETIC 40mg tablets
b31g.	*FRUSID 40mg tablets
b31h.	*LASIX 20mg tablets
b31i.	*LASIX 40mg tablets
b31j.	*LASIX 500mg tablets
b31k.	LASIX PAEDIATRIC 1mg/1mL liquid
b31l.	LASIX 20mg/2mL injection
b31m.	*LASIX 50mg/5mL injection

ReadCode	Rubric
b31n.	*LASIX 250mg/25mL injection
b31o.	*FRUMAX 40mg tablets
b31p.	*RUSYDE 20mg tablets
b31q.	*RUSYDE 40mg tablets
b31r.	FUROSEMIDE 20mg/5mL sugar free solution
b31s.	FUROSEMIDE 40mg/5mL sugar free solution
b31t.	FUROSEMIDE 50mg/5mL sugar free solution
b31u.	FUROSEMIDE 50mg/5mL injection
b31x.	*FRUSEMIDE 1mg/1mL liquid
b31y.	FUROSEMIDE 20mg/2mL injection
b31z.	FUROSEMIDE 250mg/25mL injection
b32..	BUMETANIDE
b321.	*BURINEX 1mg tablets
b322.	*BURINEX 5mg tablets
b323.	*BURINEX 1mg/5mL liquid
b324.	*BURINEX 1mg/2mL injection
b325.	*BURINEX 2mg/4mL injection
b326.	*BURINEX 5mg/10mL injection
b327.	*BETINEX 1mg tablets
b328.	*BETINEX 5mg tablets
b32u.	BUMETANIDE 1mg tablets
b32v.	BUMETANIDE 5mg tablets
b32w.	BUMETANIDE 1mg/5mL liquid
b32x.	*BUMETANIDE 1mg/2mL injection
b32y.	BUMETANIDE 2mg/4mL injection
b32z.	*BUMETANIDE 5mg/10mL injection
b33..	ETACRYNIC ACID
b331.	*EDECRIN 50mg tablets
b332.	*EDECRIN 50mg injection
b33y.	*ETHACRYNIC ACID 50mg tablets
b33z.	ETHACRYNIC ACID 50mg injection
b34..	PIRETANIDE
b341.	*ARELIX 6mg m/r capsules
b34z.	*PIRETANIDE 6mg m/r capsules
b35..	TORASEMIDE
b351.	TOREM 2.5mg tablets
b352.	TOREM 5mg tablets
b353.	TOREM 10mg tablets
b354.	*TOREM 10mg/2mL injection
b355.	*TOREM 20mg/4mL injection
b356.	TORASEMIDE 2.5mg tablets
b357.	TORASEMIDE 5mg tablets
b358.	TORASEMIDE 10mg tablets
b359.	*TORASEMIDE 10mg/2mL injection
b35A.	*TORASEMIDE 20mg/4mL injection

ReadCode	Rubric
b91b.	BUMETANIDE+POTASSIUM 500micrograms/7.7mmol m/r tablets
b91d.	FRUSEMIDE+POTASSIUM 40mg/8mmol m/r tablets
b91f.	FUROSEMIDE+POTASSIUM 20mg/10mmol m/r tablets
b91g.	FRUSEMIDE tablets+POTASSIUM m/r tablets 40mg/10mmol pack
b911.	*BRINALDIX K tablets
b912.	*BURINEX K tablets
b914.	*DIUMIDE-K CONTINUS tablets
b917.	*LASIKAL tablets
b918.	LASIX+K tablets 30day-CP combination pack

Non-steroidal anti-inflammatories:

ReadCode	Rubric
j2	NSAID
di8	NAPROXEN SODIUM
mt1	DICLOFENAC SODIUM [ACTINIC KERATOSIS]
dl6	TOLFENAMIC ACID
o4a	KETOROLAC TROMETAMOL
j2c..	NAPROXEN
j26..	FENOPROFEN [MUSCULOSKELETAL USE]
j2a..	KETOPROFEN
j2g..	TIAPROFENIC ACID
j22..	DICLOFENAC SODIUM
j2o..	DICLOFENAC SODIUM 2
j2r..	DICLOFENAC POTASSIUM
j2m..	ACECLOFENAC
j24..	ETODOLAC
j27..	FLURBIPROFEN
j2q..	DEXKETOPROFEN
j2g..	TIAPROFENIC ACID
j28..	IBUPROFEN [MUSCULOSKELETAL USE]
j2p..	IBUPROFEN [MUSCULOSKELETAL USE 2]
j2t..	DEXIBUPROFEN
j2q..	DEXKETOPROFEN
j29..	INDOMETHACIN
j2b..	MEFENAMIC ACID [MUSCULOSKELETAL USE]
j2n..	MELOXICAM
j2k..	NABUMETONE
j2d..	PHENYLBUTAZONE
j2e..	PIROXICAM
j2f..	SULINDAC
j2l..	TENOXICAM
jA3..	PARECOXIB
jA5..	ETORICOXIB

ReadCode	Rubric
jA2..	CELECOXIB

Other Nephrotoxics:

ReadCode	Rubric
f32..	CHLORPROPAMIDE
d6...	LITHIUM SALTS
fo2..	PAMIDRONATE DISODIUM

Thiazide diuretics:

ReadCode	Rubric
b2...	THIAZIDE DIURETICS
b21..	BENDROFLUMETHIAZIDE
b211.	BENDROFLUMETHIAZIDE 2.5mg tablets
b212.	BENDROFLUMETHIAZIDE 5mg tablets
b213.	APRINOX 2.5mg tablets
b214.	APRINOX 5mg tablets
b215.	*BERKOZIDE 2.5mg tablets
b216.	*BERKOZIDE 5mg tablets
b217.	*CENTYL 2.5mg tablets
b218.	*CENTYL 5mg tablets
b219.	NEO-NACLEX 5mg tablets
b21A.	*NEO-BENDROMAX 2.5mg tablets
b21B.	*NEO-BENDROMAX 5mg tablets
b21a.	*URIZIDE 5mg tablets
b21b.	NEO-NACLEX 2.5mg tablets
b22..	CHLOROTHIAZIDE
b221.	*SALURIC 500mg tablets
b222.	DIURIL 250mg/5mL oral suspension
b22y.	CHLOROTHIAZIDE 250mg/5mL oral suspension
b22z.	*CHLOROTHIAZIDE 500mg tablets
b23..	CHLORTALIDONE
b231.	HYGROTON 50mg tablets
b232.	*HYGROTON 100mg tablets
b23y.	CHLORTALIDONE 50mg tablets
b23z.	*CHLORTHALIDONE 100mg tablets
b24..	CLOPAMIDE [INGREDIENT see bdek]
b25..	CYCLOPENTHIAZIDE
b251.	NAVIDREX 500micrograms tablets
b25z.	CYCLOPENTHIAZIDE 500microgram tablets
b26..	HYDROCHLOROTHIAZIDE
b261.	*ESIDREX 25mg tablets
b262.	*ESIDREX 50mg tablets

ReadCode	Rubric
b263.	*HYDROSALURIC 25mg tablets
b264.	*HYDROSALURIC 50mg tablets
b26y.	HYDROCHLOROTHIAZIDE 50mg tablets
b26z.	HYDROCHLOROTHIAZIDE 25mg tablets
b27..	HYDROFLUMETHIAZIDE
b271.	*HYDRENOX 50mg tablets
b27z.	HYDROFLUMETHIAZIDE 50mg tablets
b28..	INDAPAMIDE
b281.	NATRILIX 2.5mg tablets
b282.	*NINDAXA 2.5mg tablets
b283.	*NATRAMID 2.5mg tablets
b284.	*OPUMIDE 2.5mg tablets
b285.	INDAPAMIDE 1.5mg m/r tablets
b286.	NATRILIX SR 1.5mg m/r tablets
b287.	ETHIBIDE XL 1.5mg m/r tablets
b288.	INDIPAM XL 1.5mg m/r tablets
b289.	MAPEMID XL 1.5mg m/r tablets
b28z.	INDAPAMIDE 2.5mg tablets
b29..	MEFRUSIDE
b291.	*BAYCARON 25mg tablets
b29z.	*MEFRUSIDE 25mg tablets
b2a..	*METHYCLOTHIAZIDE
b2a1.	*ENDURON 5mg tablets
b2az.	*METHYCLOTHIAZIDE 5mg tablets
b2b..	METOLAZONE
b2b1.	*METENIX-5 5mg tablets
b2b2.	*XURET 500micrograms tablets
b2b3.	METOLAZONE 500micrograms tablets
b2bz.	*METOLAZONE 5mg tablets
b2c..	POLYTHIAZIDE
b2c1.	*NEPHRIL 1mg tablets
b2cz.	*POLYTHIAZIDE 1mg tablets
b2d..	XIPAMIDE
b2d1.	DIUREXAN 20mg tablets
b2dz.	XIPAMIDE 20mg tablets
b913.	*CENTYL K m/r tablets
b915.	*ESIDREX K tablets
b916.	HYGROTON K tablets combination pack
b919.	*NAVIDREX-K tablets
b91a.	NEO-NACLEX-K tablets
b91e.	CHLORTHALIDONE tablets+POTASSIUM m/r tablets 25mg/6.7mmol pack
b91h.	BENDROFLUMETHIAZIDE+POTASSIUM 2.5mg/8.4mmol m/r tablets
bkI..	OLMESARTAN+AMLODIPINE+HYDROCHLOROTHIAZIDE
bkI1.	SEVIKAR HCT 20mg/5mg/12.5mg tablets

ReadCode	Rubric
bkI2.	SEVIKAR HCT 40mg/5mg/12.5mg tablets
bkI3.	SEVIKAR HCT 40mg/10mg/12.5mg tablets
bkI4.	SEVIKAR HCT 40mg/5mg/25mg tablets
bkI5.	SEVIKAR HCT 40mg/10mg/25mg tablets
bkC..	HYDROCHLOROTHIAZIDE + OLMESARTAN
bkC1.	OLMETEC PLUS 20mg/12.5mg tablets
bkC2.	OLMETEC PLUS 20mg/25mg tablets
bkC3.	OLMETEC PLUS 40mg/12.5mg tablets
bkCx.	OLMESARTAN+HYDROCHLOROTHIAZIDE 40mg/12.5mg tablets
bkCy.	OLMESARTAN + HYDROCHLOROTHIAZIDE 20mg/25mg tablets
bkCz.	OLMESARTAN + HYDROCHLOROTHIAZIDE 20mg/12.5mg tablets
bk5x.	IRBESARTAN+HYDROCHLOROTHIAZIDE 300mg/25mg tablets
bk5y.	IRBESARTAN+HYDROCHLOROTHIAZIDE 300mg/12.5mg tablets
bk5z.	IRBESARTAN+HYDROCHLOROTHIAZIDE 150mg/12.5mg tablets
bk8w.	TELMISARTAN+HYDROCHLOROTHIAZIDE 80mg/25mg tablets
bk8x.	TELMISARTAN+HYDROCHLOROTHIAZIDE 40mg/12.5mg tablets
bk8y.	TELMISARTAN+HYDROCHLOROTHIAZIDE 80mg/12.5mg tablets
bk4x.	VALSARTAN+HYDROCHLOROTHIAZIDE 80mg/12.5mg tablets
bk4y.	VALSARTAN+HYDROCHLOROTHIAZIDE 160mg/25mg tablets
bk4z.	VALSARTAN+HYDROCHLOROTHIAZIDE 160mg/12.5mg tablets
bk3y.	LOSARTAN POTASSIUM+HYDROCHLOROTHIAZIDE 100mg/12.5mg tablets
bk3z.	LOSARTAN POTASSIUM+HYDROCHLOROTHIAZIDE 100mg/25mg tablets
bi1e.	CAPTOPRIL+HYDROCHLOROTHIAZIDE 25mg/12.5mg tablets
bi1f.	CAPTOPRIL+HYDROCHLOROTHIAZIDE 50mg/25mg tablets
bi2b.	ENALAPRIL MALEATE+HYDROCHLOROTHIAZIDE 20mg/12.5mg tablets
bi3p.	LISINOPRIL+HYDROCHLOROTHIAZIDE 20mg/12.5mg tablets
bi3t.	LISINOPRIL+HYDROCHLOROTHIAZIDE 10mg/12.5mg tablets
bi48.	QUINAPRIL+HYDROCHLOROTHIAZIDE 10/12.5mg tablets
bi4F.	QUINAPRIL+HYDROCHLOROTHIAZIDE 20mg/12.5mg tablets
bi55.	PERINDOPRIL ERBUMINE+INDAPAMIDE 4mg/1.25mg tablets
bi69.	RAMIPRIL 2.5mg+5mg+10mg capsules titration pack
biC8.	PERINDOPRIL ARGININE+INDAPAMIDE 5mg/1.25mg tablets

APPENDIX 15: PROCESSED CLINICAL VARIABLES FROM SIR DATASET (CHAPTER 4)

Pulse Pressure:
Formula: Diastolic Blood Pressure – Systolic Blood Pressure

Hypertension:
Systolic BP >140
OR
Diastolic BP >90

BMI:
Formula: Weight in kg x (Height in m)^2

Log^10 Creatinine:
Formula: log^10 each creatinine value

MDRD eGFR:
MDRD formula = 175 * (creatinine in umol.L / 88.4)^-1.154 * age^-0.203 [* 0.742 if female] [*1.212 if black]

CKD-EPI eGFR:
eGFR = 141*(creatinine in umol.L / k, 1)^a * (creatinine in umol.L / k, 1)^-1209 * 0.993^age [* 1.018 if female] [*1.159 if black]
where a = -0329 if female and -0.411 if male
where k = 61.9 if female and 79.6 for males

Chronic Kidney Disease Criteria (based on eGFR):
First Diagnosis: eGFR < 60 for over 6 months
CKD stage 3a: eGFR 45 - 59
CKD stage 3b: eGFR 30 - 44
CKD stage 4: eGFR 15 - 29
CKD stage 5: eGFR <15

Anaemia:
Male: Hb < 130
Female: Hb < 115

APPENDIX 16: PRE-FEATURE SELECTION COLUMN EXCLUSIONS (CHAPTER 4)

Variable column excluded	Reason
AFDate	Redundant; used to create DaysSinceAF column
Age	Used as constant
AnnualPerc_CKDEPI	Derived from creatinine
AnnualPerc_crea	Derived from creatinine
AnnualPerc_MDRD	Derived from creatinine
BirthYear	Dates incompatible with feature selection
BMIDateFlag	Identifies date-flags only
BNP	SIR 97% missing
BNP_DF	SIR 97% missing
BNPDateFlag	Identifies date-flags only
BUNDateFlag	Identifies date-flags only
CKDDate	Dates incompatible with feature selection
CKDEPIeGFR	Derived from creatinine
CKDGStage	Redundant; replaced by CustomeGFR
CKDStage_MDRDeGFR	Derived from creatinine
CKDStage_CKDEPIeGFR	Derived from creatinine
CKDStage3to5_MDRDeGFR	Derived from creatinine
CKDStage_instant_MDRDeGFR	Derived from creatinine
CKDStage3to5_CKDEPIeGFR	Derived from creatinine
CKDStage_instant_CKDEPIeGFR	Derived from creatinine
CLD	>90% missing
CLDDate	>90% missing
CodeValue	Same as creatinine
CodeUnits	Redundant
DaysSinceNephrectomy	>90% missing
DaysSinceCLD	>90% missing
DaysSinceRenMal	>90% missing
DaysSinceRT	>90% missing
DBPDateFlag	Identifies date-flags only
DBP_DF	Date flagged data
DiabDate	Redundant; used to create DaysSinceDiabetic
Death	Data incompatible with longitudinal regression
DeathDate	Dates incompatible with feature selection
EntryDate	Dates incompatible with feature selection
event.date	Dates incompatible with feature selection
eventYear	Dates incompatible with feature selection
Haemoglobin_DF	Date flagged data
HaemDateFlag	Identifies date-flags only
HeartRate	>80% missing
HeartRateDateFlag	Identifies date-flags only
HeartRate_DF	Date flagged data
IHDDate	Identifies date-flags only
LSOA	Used to process IMD_Decile2010

Variable column excluded	Reason
MaritalStatus	Not used in clustering
MatDate1	Not used in clustering
MatDate2	Not used in clustering
EstPregnant	Not used in clustering
MCVDateFlag	Identifies date-flags only
MCV_DF	Date flagged data
MDRDeGFR	Derived from creatinine
Nephrectomy	>90% missing
NephrectomyDate	>90% missing
No AKI episodes	Derived from creatinine
NTPROBNP	SIR 99% missing
NTPROBNP_DF	SIR 99% missing
NTPROBNPDateFlag	Identifies date-flags only
PVDDate	Redundant; used to create DaysSincePVD
Renal malignancy	>90% missing
RenalTransplant	>90% missing
ReligionDescription	>90% missing
ReadCode	Redundant
RMALDate	>90% missing
RRD_CKDEPI	Derived from creatinine
RRD_Creatinine	Derived from creatinine
RRD_MDRD	Derived from creatinine
RTDate	>90% missing
RRTDate	Redundant; used to create DaysSinceRRT
SBPDateFlag	Identifies date-flags only
SBP_DF	Date flagged data
SerPotDateFlag	Identifies date-flags only
SerPotassium_DF	Date flagged data
SerSodDateFlag	Identifies date-flags only
SerumSodium_DF	Date flagged data
SerumAlbuminDateFlag	Identifies date-flags only
SerumAlbumin_DF	Date flagged data
Source	Used for de-duplication
UACDateFlag	Identifies date-flags only
UACratio	>40% missing
UACratio_DF	Date flagged data
UricAcid	SIR 62% missing
UricAcid_DF	SIR 62% missing
UricAcidDateFlag	Identifies date-flags only
Urine Albumin	>40% missing
UrineAlbuminDateFlag	Identifies date-flags only
UrineAlbumin_DF	Date flagged data

APPENDIX 17: INCLUDED COLUMNS IN FEATURE SELECTION VARIABLE SET (CHAPTER 4)

Variable	Description	Accepted value range applied	Range	Units in final table	Records available	% indicators missing
ACE_Inhibitors	Ace inhibitor daily dosage	no restrictions	categorical	see lookup (values in mg)	53424	NA
AF	Atrial fibrillation code in history	0-1	0-1	binary	1219	NA
Age	age to nearest year	no restrictions	17-103	years	208225	0
Anaemia	Based on Hb – lookback to last Hb	0-1	0-1	binary	119050	NA
BMI	Mean daily body mass index	10 – 70 kg/m^2	10.6-68.7	kg/m^2	203439	2.3
BUN	Mean daily Blood urea (inc. blood urea nitrogen)	1 – 50 mmol/L	0-31.3	mmol/L	208214	<0.01
DaysSinceAF	Days since first atrial fibrillation code recorded	no restrictions	0-5812	integer	1219	NA
DaysSinceDiabetic	Days since first diabetes related code recorded	no restrictions	0-8987	integer	73469	NA
DaysSinceIHD	Days since first IHD related code recorded	no restrictions	0-6683	integer	1056	NA
DaysSincePVD	Days since first PVD related code recorded	no restrictions	0-9467	integer	1300	NA
DaysSinceRRT	Days since first RRT related code recorded	no restrictions	0-9357	integer	5509	NA
DBP	Min daily diastolic BP	20-200 mm/Hg	22-173	mm/Hg	206665	0.75
Diabetes	Diabetes indicative codes recorded/not recorded	0-1	0-1	binary	73469	NA
Ethnicity	Coded ethnicity	no restrictions	1:6	categorical	35	<0.01
Gender	gender	M/F	string	categorical	208225	0
Haemoglobin	Mean daily Haemoglobin	30 – 260 g/L	30-225	g/L	207423	0.3
hfage	age (yrs) at first hf diagnostic code in all data	18+	18-102	integer	208225	0
hfdate	Index date of heart failure diagnosis					
HTN	Based on BP values	no restrictions	0-1	binary	47149	NA
IHD	Ischaemic heart disease (syn. angina, myocardial imfarction, coronary artery disease, coronary heart disease)	no restrictions	0-1	binary	1056	NA

Variable	Description	Accepted value range applied	Range	Units in final table	Records available	% indicators missing
IMD_Decile2010	IMD decile, rank 2010 values	1-10 (1=most deprived)	1-10	integer	206423	0.9
Immunosuppressants	Immunosuppressant daily dosage	no restrictions	categorical	see lookup (values in mg)	1944	NA
log_crea	log creatinine	no restrictions	1.3-3.1	umol/L	208225	0
Loop_Diuretics	Loop diuretics daily dosage	no restrictions	categorical	see lookup (values in mg)	80648	NA
MCV	Mean daily mcorpuscular volume	50 – 150 fL	50.9-144.7	fL	207802	0.2
NoAKIepisodes	Number of prior AKI episodes- AKI counted even if patient has a simultaneous CKD diagnosis	no restrictions	0-20	count	136663	NA
PatientID	Pseudonymised identifying code	no restrictions	1-21246	categorical	208225	0
PP	Pulse pressure (SBP-DBP)	>=0	0-200	bpm	206551	0.8
PracticeID	Individual GP practice code. Used for splitting.					
PVD	PVD related code present prior to/with test	0-1	0-1	binary	1300	NA
RRT	Any RRT related code recorded for this patient	0-1	0-1	binary	5509	NA
SBP	Min daily systolic BP	30-300 mm/Hg	33-276	mm/Hg	206665	0.7
SerPotassium	Mean daily serum potassium	2 – 10 mmol/L	2-10	mmol/L	208202	<0.01
SerumAlbumin	Mean daily serum albumin	10 – 60 g/L	10-60	g/L	208053	<0.01
SerumSodium	Mean daily serum sodium	80 – 200 mmol/L	102.8-179.0	mmol/L	208218	<0.01
Smoker	Smoking status to date	0-1 never smoker/ever smoker	0-1	binary	30116	NA
TimeSincehf	Time since heart failure – use as time effect in model					
[All drug columns]	Individual and category drug columns					