A palliative care approach for people with advanced heart failure: recognition of need, transitions in care and impact on patients, family carers and clinicians

Short title: Palliative care and advanced heart failure

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Abstract

Background: Despite international and national consensus guidelines, patients with advanced heart failure (HF) have significant unmet palliative care needs. UK policy recommends identification of those requiring palliative care based on prognosis (last year of life). However, HF has an unpredictable course, and clinicians might not discuss a palliative approach for fear of causing alarm and destroying hope.

Aim: To explore aspects of a palliative care approach for people with advanced HF: recognition of need, transitions in care and impact on patients, family carers and clinicians

Methods: Mixed method study with integration of findings. Systematic literature review of prognostic variables associated with the last year of life in HF. Analysis of General Practice Research Database (GPRD) records to compare recognition of the need for palliative care between cancer and HF patients. Qualitative semi-structured interviews with patients receiving a palliative approach to care, their carers and clinicians.

Findings: GPRD data demonstrated gross inequity between documented recognition of the need for a palliative care approach; HF patients were poorly represented on the palliative care register, and those that were, were registered close to death. Prognostic markers, identified in both the systematic review and GPRD, had limited clinical usefulness for identifying the last year of life. From interview data, clinicians appeared reluctant to discuss a palliative care approach without clear irreversible deterioration of the patient. However, patients welcomed, and some initiated, conversations regarding the change in focus of care. Following such discussion all involved found this approach beneficial, even with subsequent periods of stability or improvement. Other barriers included lack of recognition of symptoms by clinicians and difficulties in delivering proactive care.

Conclusions: A palliative care approach before the very end of life is beneficial in this group. A problem-based flexible approach to recognising the need for palliative care, rather than prognosis is recommended.

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Author's Declaration

'I confirm that this work is original and that if any passage(s) or diagram(s) have been copied from academic papers, books, the internet or any other sources these are clearly identified by the use of quotation marks and the reference(s) is fully cited. I certify that, other than where indicated, this is my own work and does not breach the regulations of HYMS, the University of Hull or the University of York regarding plagiarism or academic conduct in examinations. I have read the HYMS Code of Practice on Academic Misconduct, and state that this piece of work is my own and does not contain any unacknowledged work from any other sources. I confirm that any patient information obtained to produce this piece of work has been appropriately anonymised.'

Publications, presentations and prizes

Publications

Gadoud A, Johnson MJ. Models of palliative care in advanced heart failure. *MIMS Oncology and Palliative Care*. 2010;4(2):30-2. (from chapter one)

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Gadoud A, Taylor P, Hussain JA. How to appraise a qualitative study. *British Journal of Hospital Medicine (London)*. 2013;74(5):271-4. (from chapter five)

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Oral presentation

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Invited presentations

11 May 2011 How can we improve access to palliative care for people with heart failure? North East Yorkshire and North Lincolnshire Comprehensive Local Research Network Palliative Care Specialty Group Conference, the Royal York Hotel, York (from chapter one and two)

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1 Heart failure and palliative care

1.1 Introduction

Despite international and national consensus guidelines that recommend a palliative care approach and access to palliative services for people with advanced heart failure, patients still have significant unmet palliative care needs.

The thesis will explore a palliative care approach for people with advanced heart failure:

(i) recognition of need

(ii) transitions in care

(iii) impact on patients, family carers and clinicians.

This chapter starts the exploration with a definition of palliative care, followed by a discussion of policy and research literature relating to heart failure and palliative care. The World Health Organisation (WHO) definition of palliative care will be used and then expanded to include current evidence and historical, societal and philosophical underpinnings of this type of care. United Kingdom (UK) health care policy regarding palliative care for patients with advanced heart failure will be described. The relevant literature will be reviewed to provide a summary of the key issues with regard to palliative care for patients with heart failure; why palliative care for heart failure patients is important, and current barriers and facilitators to its implementation. This chapter will conclude with the identified gaps in the current literature regarding this approach to care.

1.2 A palliative approach to care generally and specifically in advanced heart failure

1.2.1 Definitions of palliative care

The WHO, 2002 definition of palliative care is:

> …an approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness… is applicable early in the course of illness, in conjunction with other therapies that are intended to prolong life…[1(pp. 94-95)]

The important aspects of this definition for this thesis is that it is *an approach to care* rather than a medical speciality, a building such as a hospice, a particular intervention or an individual such as a Macmillan nurse.

In the UK, palliative care is delivered by the professionals responsible for the day to day health and social care of the patient and family, and by informal carers who may be members of that family. This type of care is referred to as **general or generalist palliative care. Specialists in palliative care** may also provide care. These are health and social care professionals, for whom palliative care is their main area of practice and who may have undergone further specialist training[2].

Notably this definition encompasses any *life limiting illness* rather than just one condition such as cancer. In the UK specialist palliative care services have strong links with the voluntary sector, have traditionally been funded by cancer charities and have links with cancer services. They are used less frequently by patents with non-cancer palliative conditions[3].

A palliative care approach can occur alongside disease modifying therapies, rather than waiting until these therapies are discontinued. In the past it was thought palliative care was only required in the last few days and weeks of life but now it is recognised that a palliative care approach should be offered alongside curative treatment, with a gradual increase in palliative care as the disease progresses and active treatment is withdrawn[4]. However, even in oncology this pattern of a gradual increase in palliative care as disease progresses is not always appropriate. A systematic review describes three main approaches: a sharp transition point, a phased transition and a simultaneous care approach[5].

An integrated approach is recommended in European and United States (US) guidelines[6, 7]. This is provision of palliative and supportive care along with disease modifying interventions as part of comprehensive heart failure care. Goodlin, author of the US guidelines, describes five stages of heart failure care from initial symptoms to end of life (see **figure 2).** She describes how at each stage there are heart failure interventions, decision making/advance care planning, and supportive care (communication, education, psychosocial and spiritual issues, and symptom management). Despite having five stages, the stages are not consecutive: sudden

death can occur at any point along the disease trajectory and transplant and other acute interventions can put a patient back to an earlier stage[8].

Authors of a recent systematic review of randomised controlled trials (RCTs) identify a further problem; there is no clear definition of "a palliative care population." The starting point of this review is the WHO definition of palliative care but the authors concludes that it is vague and lacking in detail, resulting in significant variation in definition of the palliative care patient in practice, policy and research. The authors of the systematic review suggest that the following key elements should be included in the definition of a palliative care patient[9]:

- Disease trajectory: specifically the WHO definition above mentions "life-threatening" disease[1], whereas other definitions may be progressive, incurable, far advanced or just advanced, life threatening and/ or active
- The type of disease and its progression: not only cancer but other diseases such as organ failure, dementia, neurodegenerative diseases, AIDS and stroke. However, not all patients would be considered a palliative care patient and so a qualifier is needed such as advanced disease, rate of disease progression, whether progression can be slowed, and/ or the absence of therapies with a curative intent.
- Approach and outcomes to care: receiving complex interventions that reflect holistic and multidisciplinary care with a variety of outcomes and with an emphasis on symptom control and quality of life.
- Other elements: the subjective judgement of the physician of the palliative care status of the patient, for example, by use of "the surprise question". The authors also propose that the patient's choice and or readiness to accept palliative care should also be considered important in a definition. Based on qualitative work not yet published the authors propose patients' readiness and a vision of a palliative care shared by the patient and all caregivers involved to be potentially important elements in the definitions of a palliative care patient[9].

1.2.2 **Historical, societal and philosophical aspects of palliative care**

An additional aspect of palliative care is the historical, societal and philosophical underpinnings of this type of care. The modern hospice and palliative care

movement in the UK began in the 1950s and 1960s under the leadership of Dame Cicely Saunders. Cicely Saunders used the term "total pain" to describe the holistic care of the new discipline, with its emphasis on symptom control and quality of life[10]. The movement is described as affirming life and seeing death as a natural process[1]. A significant societal influence at that time was the medicalisation of dying and the movement of death from home to hospitals. Usual practice at that time was that a cancer diagnosis and prognosis was rarely discussed with patients. There was neglect, particularly from medical staff towards the care of the dying, resulting in distress for dying patients due to poor symptom control, lack of dignity and attention to the psychosocial aspects of care and problems associated with communication and disclosure of information about dying[10-15].

An important concept in hospice and palliative care is that of "the good death." A good death is subjective and hence different for each individual. This means there is no one definition of a good death and it has changed as a concept over time. For example, "the good death" historically was associated with religious values[16] and more recently it has been used by the pro euthanasia movement. Pro-euthanasia groups would describe euthanasia as a good death as it respects individual choice and autonomy[17]. Descriptions of a good death from studies of patients demonstrate themes of receiving adequate pain and symptom management, avoiding inappropriate prolongation of dying, achieving a sense of control, relieving burden, and strengthening relationships with loved ones as important[18, 19]. Palliative care is often seen to promote the ideas of and influenced by the work of Glaseur and Strauss and Kubler-Ross with the ideas of "open awareness" and "acceptance" of impending death. This is mirrored in the patient studies described above: being mentally aware, having funeral and other arrangements organised, an ability to resolve unfinished business and make peace with God are seen as important by patients. However, some perceive this implies there is an opposite "the bad death", where there is lack of acceptance of death by patients or patients' families, or a failure to actively pursue fulfilment of living until the final stages of dying and these are seen as less acceptable death by those in the palliative care movement[17]. The hospice and palliative care movement emphasises the importance of individualised care for patients wherever they are on their personal trajectory and not forcing patients into open awareness or acceptance. This important concept, of

individualised care, allows opportunities for conversations for those who wish to discuss and plan their impending death and respects patients' autonomy and independence[17]. Within this idea of "the good death", there is an important element of planning and proactive care within palliative care, but only for those who wish this approach. Recent government policy reflects this strongly, particularly with regard to preferred place of care and death[15], see also **section 1.3** and **section 1.6.1.** However, this can be seen as a narrow view as proactive care and planning is wider than this, extending to explore patients' wishes about other aspects of their care and other issues that are important to them. Respect for patients' informed wishes enables their involvement in decision making[15]. It is important to note that patients' views and wishes may change over time, for example as systematic review has shown about 20% of patients change their mind as death approaches[20].

It has been proposed that the current situation with advanced heart failure is similar to the time when the diagnosis and prognosis of cancer was not discussed openly with patients[21]. With the latter progress has been made but the reluctance to talk about dying persist for the former. This can lead to complex interactions between the doctor, the person with heart failure and their families as they avoid talking about death, which often causes distress and isolation[22, 23].

1.3 UK health care policy regarding palliative care for patients with advanced heart failure

Different models of palliative care have developed in different countries. For example to be eligible for hospice care(generally home care) funding with Medicare, Medicaid and most private insurers in the US, patients require a physician to confirm that they have a prognosis of six months or less[24, 25]. This thesis will focus on United Kingdom (UK) palliative care but will include international literature, where findings are generalisable across countries with different models of palliative and other health and social care services.

The National Service Framework for coronary heart disease, published in 2000, was the first UK health care policy document to state that patients with advanced heart failure should have access to palliative care services[23, 26]. The discussion in the document was brief and lacked specific detail. In 2003, the National Institute for

Clinical Excellence (NICE) produced guidelines on the management of chronic heart failure, which included a section on palliative care. These were updated in 2010, although there were no changes to the palliative care sections[27]. NICE recommended good communication with patients and their carers and stated that prognosis "should be discussed with patients and carers in a sensitive, open and honest manner"[27]. It recognised that further research is required before methods for estimating prognosis could be recommended. End of life care and palliative care was seen as important, but due to lack of more robust evidence, the recommendations were at the "good practice point" level of evidence, which was a consensus from the clinical experience of the guidelines group[27]. Following on from the 2010 NICE guidelines quality standards were produced relating to diagnosis, assessment and management of chronic heart failure, see **figure1**.

5 People with chronic heart failure are offered personalised information, education, support and opportunities for discussion throughout their care to help them understand their condition and be involved in its management, if they wish.
6 People with chronic heart failure are cared for by a multidisciplinary heart failure team led by a specialist and consisting of professionals with appropriate competencies from primary and secondary care, and are given a single point of contact for the team.
9 People with stable chronic heart failure receive a clinical assessment at least every 6 months, including a review of medication and measurement of renal function.
10 People admitted to hospital because of heart failure have a personalised management plan that is shared with them, their carer(s) and their GP.
11 People admitted to hospital because of heart failure receive input to their management plan from a multidisciplinary heart failure team.
12 People admitted to hospital because of heart failure are discharged only when stable and receive a clinical assessment from a member of the multidisciplinary heart failure team within 2 weeks of discharge.
13 People with moderate to severe chronic heart failure, and their carer(s), have access to a specialist in heart failure and a palliative care service.

Figure 1. Selected NICE quality standards for chronic heart failure relevant to the thesis, numbered as in original document, therefore not sequential

In 2003 the *Building on the Best* White Paper set out plans to improve choice within the NHS including a programme to improve end of life care. This programme, the NHS End of Life Care Programme, was renamed National End of Life Care

Programme. Most recently (April 2013), it was incorporated within the NHS Improving Quality programme. All these initiatives encourage implementation of tools such as the Gold Standards Framework (GSF)[28], Liverpool Care Pathway for the Dying Patient[29] and the Preferred Priorities for Care[30]; tools based on cancer palliative care but which have been adapted for use for non-malignant conditions[15]. The GSF, initially designed for and mostly used in primary care, is a systematic approach to identify, assess and plan the care of patients in the 12 months of life. The Liverpool Care Pathway is a document to promote good practice for the care of patients in the last days of life. Following a recent review the Liverpool Care Pathway is being phased out to be replaced by individualised care plans[31]. The Preferred Priorities for Care is a document which allows patients to discuss and record their preferences for end of life care.

In 2008 the end of life care strategy was published in England[32]. One of the key features of this document was a significant shift in focus from oncology palliative care only to provision of palliative care regardless of diagnosis[33]. Despite this, the content is still largely based on experiences from cancer palliative care but describes a "palliative care pathway " which incorporates the following stages: identification of people approaching the end of life; initiating discussions about preferences for end of life care; through to care for the last days of life and bereavement care (see **figure 5**)[32]. The strategy was broadly welcomed by specialist palliative care[34] but some criticism was levelled at its uncritical promotion of cancer models to other life limiting illnesses[23]. Another aspect of the end of life care strategy is that it emphases the role of generalists in delivering the majority of palliative care with specialist palliative care being available for difficult or refractory problems[2].

A document describing a care pathway for end of life care for advanced heart failure patients was published in 2010, as part of the end of life care strategy[35]. This care pathway is similar to that in the original strategy of 2008 but also incorporates the model of care described by Goodlin the author of the US guidelines described in **section 1. 2.1** and **figure 2**[8].

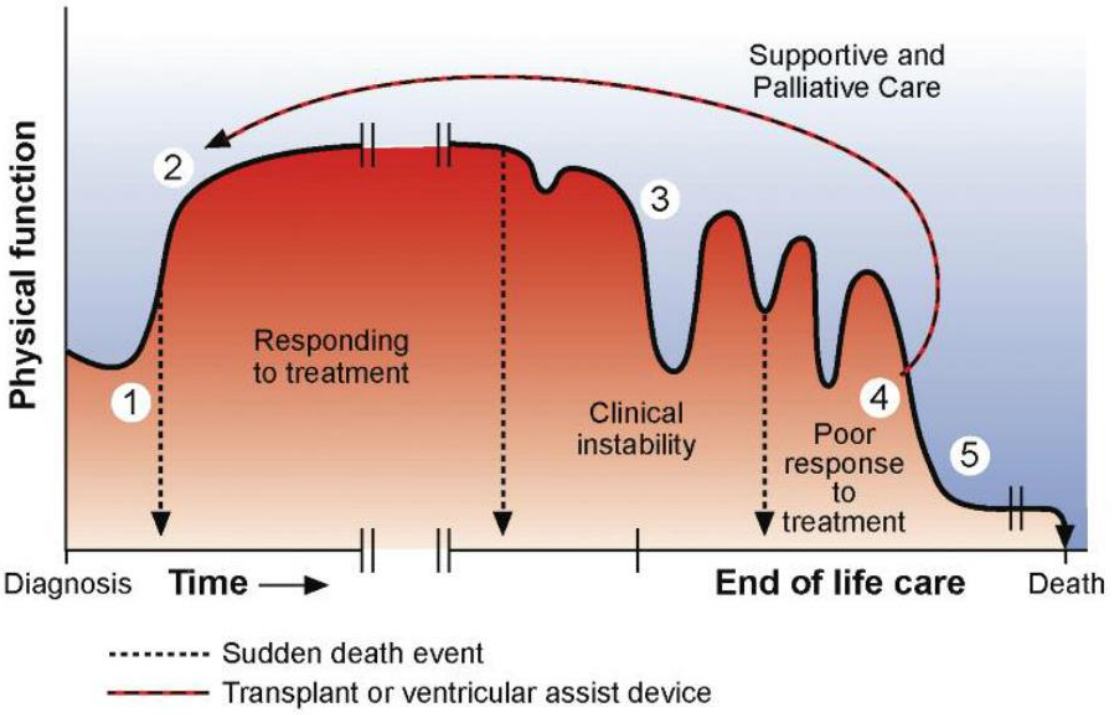

Figure 2. The typical course of heart failure. The typical course of heart failure. Phase1 symptom onset, diagnosis and initiation of treatment; phase 2 plateau period; phase 3; periods of instability with recurrence of symptoms linked to deterioration in heart function; phase 4 increasing symptoms and exhibiting declining physical capacity, despite optimal therapy; phase 5 last days of life. The course of heart failure and the time spent progressing through these illness phases is very variable and it is important to emphasise that clinical deterioration and death may occur at any time[8, 35].

Health care policy has changed emphasis due to an altered economic climate, aiming to improve care more efficiently[36]. The Quality, Innovation, Productivity and Prevention (QIPP) collection is about quality at a time of economic difficulty. Interestingly, a case study from Northampton reported as an example from a pilot site was about early identification of patients with heart failure in the last year of life but this proved too difficult and the project has concentrated on those patients nearer the end of their life[37]. Further discussion regarding the cost of end of life care is discussed in **section 1.6.1.**

A government commissioned review into the way palliative care is funded also describes phases in a patient's illness as shown in **figure 3**. These are stable, deteriorating, unstable and dying. Importantly it emphasises that these phases are not linear, can be repeated and are variable in length. This means periods of stability, can and do occur[38].

Phase of illness
Phase of illness refers to a phase in the patient's illness reflecting the type and level of care needed. Four main phases can be identified:

Stable: symptoms controlled, needs met by current care plan, family situation stable
Deteriorating: symptoms gradually or steadily worsening over weeks, or development of new but expected problems over days/weeks, with need for adaptation of care plan and regular review, with worsening family distress and/or social/practical burden (note that rapidly or unpredictably deteriorating would fall into the next category)
Unstable: new severe problem(s) or rapid increase in existing severe problem(s) over days, and urgent or semi-urgent change in intervention(s) needed to meet needs
Dying: death anticipated in a matter of days, requiring frequent, usually daily, review

Throughout the course of a disease a patient will experience several phases. There is no sequential order of the phases and a patient can be in the same phase several times during their disease trajectory. Phases can vary in length from days to weeks to months.

Figure 3. Palliative care funding review-phase of illness[38]

A key theme, within many of these policies, and highly pertinent to this thesis is identification or recognition of "end of life". **Figure 4** summarises three key documents, which are discussed below:

The GSF is promoted in both the end of life care programme and the end of life care strategy. The GSF prognostic indicator guide updated in 2008 provides triggers for consideration of whether palliative and supportive care is needed by the patient and to consider whether the patient should be placed on a palliative care register **(figure 4).**The decision to place a patient on the palliative care register places heavy reliance on prognostic indicators although there is brief mention of patient choice or need as other factors that could be considered[39]. The prognostic indicator guide was updated in 2011. Although the indicators are similar the theme is now more about need than prognosis, and includes other details such as "find your 1%" i.e. those patients in the last year of life[40].

General Medical Council (GMC) guidance (2010) encourages discussion about end of life care with all patients 'approaching the end of life'; defined as all patients who

are likely to die within the next 12 months **(figure 4)**. It does not define how this group is to be identified. The guidance allows that some do not wish to talk about their future, and if so, this should be respected[41]. This again represents a significant shift in policy, moving to a default position that the patient should have full disclosure of information.

Quality standards for end of life care for adults have been produced by NICE that use the GMC, 2010, definition of end of life **(figure 4)** and specifically state that only palliative care in the last year of life is end of life care[42].

Current UK health care policy is in a state of significant change. The Health and Social Care Act 2012 introduced a radical restructuring of the NHS in England. It abolished primary care trusts (PCTs) and strategic health authorities and instead set up "clinical commissioning groups" led by General Practitioners (GPs) and opens NHS services to be commissioned by "any qualified provider"[43]. The white paper , preceding the act "Equity and Excellence: Liberating the NHS", included promotion of shared decision making "no decision about me without me" and "In end-of-life care", we will move towards a national choice offer to support people's preferences about how to have a good death, and we will work with providers, including hospices, to ensure that people have the support they need"[44]. This continues the trend towards patient's choice and preferences about their end of life care.

End of life care strategy, Gold Standards Framework- prognostic indicator guide, 2008
Three triggers for Supportive/ Palliative Care are suggested - to identify these patients we can use any combination of the following methods:
1. The surprise question 'Would you be surprised if this patient were to die in the next 6-12months' -an intuitive question integrating co-morbidity, social and other factors. If you would not be surprised, then what measures might be taken to improve their quality of life now and in preparation for the dying stage. The surprise question can be applied to years/months/weeks/days and trigger the appropriate actions at each stage i.e. "the right thing to happen at the right time"
2. Choice/ Need - The patient with advanced disease makes a choice for comfort care only, not 'curative' treatment, or is in special need of supportive / palliative care e.g. refusing renal transplant
3. Clinical indicators – Both general and specific to disease groups
Specific indicators of advanced disease for each of the three main end of life
General Predictors
Co-morbidity is increasingly the biggest predictive indicator of mortality and morbidity. Also-
- Weight loss - Greater than 10% weight loss over 6 months
- General physical decline
- Serum Albumin < 25 g/l
- Reducing performance status / ECOG/Panofsky score (KPS) < 50%. Dependence in most activities of daily living(ADLs)

Specific predictors for heart failure
At least two of the indicators below:-
- CHF NYHA stage III or IV – shortness of breath at rest or minimal exertion
- Patient thought to be in the last year of life by the care team - the 'surprise' question
- Repeated hospital admissions with symptoms of heart failure
- Difficult physical or psychological symptoms despite optimal tolerated therapy

GMC: Treatment and care towards the end of life: good practice in decision-making, 2010
Patients are 'approaching the end of life' when they are likely to die within the next 12 months. This includes patients whose death is imminent (expected within a few hours or days) and those with:
(a) advanced, progressive, incurable conditions
(b) general frailty and co-existing conditions that mean they are expected to die within 12 months
(c) existing conditions if they are at risk of dying from a sudden acute crisis in their condition
(d) life-threatening acute conditions caused by sudden catastrophic events.

NICE Quality standard topic: End of life care for adults 2011
This quality standard uses the GMC definition of people approaching the end of life from treatment and care towards the end of life: good practice in decision making: (see definition above)
Given this, any palliative care within the last 12 months of life is regarded as end of life care. It is recognised that some people will benefit from palliative care before this time. Palliative care before the last 12 months of life is not included in this definition of end of life care and is therefore outside the scope of this quality standard.

Figure 4. UK health policies regarding identification or definition of "end of life"

The terminology in the more recent policy documents has changed from palliative care to end of life care. It has been suggested that this change is to break the association between palliative care as something that happens to people with cancer and is undertaken by specialist; to care regardless of diagnosis and undertaken by generalists. As part of a larger study of palliative care management conducted in England and New Zealand, understanding of palliative care and end of life care were explored. The term palliative care was not well understood by generalist, especially with regard to a philosophy of care, rather than specific services and the role of generalists in delivering palliative care. The term "end of life care" was not understood by any of the generalists[45]. As illustrated by **figure 4**, it is also often referred to as "the last year of life" without guidance as to why that definition has been chosen or more importantly how this period can be practically identified in an individual patient**. Figure 5** demonstrates that identification is seen as the first step in end of life care followed by communication, assessment and proactive planning and delivery of care, in a structured transition to a palliative care approach[46].

End of life care strategy
Identification of people approaching the end of life and initiating discussions about preferences for end of life care;
Care planning: assessing needs and preferences, agreeing a care plan to reflect these and reviewing these regularly;
Coordination of care;
Delivery of high quality services in all locations;
Management of the last days of life;
Care after death;
Support for carers, both during a person's illness and after their death

NICE Quality standard topic: End of life care for adults 2011
Quality statement 1: **Identification**
Quality statement 2: Communication and information
Quality statement 3: Assessment, care planning and review
Quality statement 4: Holistic support – physical and psychological
Quality statement 5: Holistic support – social, practical and emotional
Quality statement 6: Holistic support – spiritual and religious
Quality statement 7: Holistic support – families and carers
Quality statement 8: Coordinated care
Quality statement 9: Urgent care
Quality statement 10: Specialist palliative care
Quality statement 11: Care in the last days of life
Quality statement 12: Care after death – care of the body
Quality statement 13: Care after death – verification and certification
Quality statement 14: Care after death – bereavement support
Other quality standards about workforce planning

Figure 5. UK policies post identification or definition of "end of life" and the consequent need for communication, assessment and proactive planning and delivery of care

1.4 Definition and epidemiology of heart failure

Heart failure is defined clinically, as a syndrome in which patients have typical symptoms such as breathlessness, ankle swelling and fatigue and signs of fluid overload resulting from a structural or functional abnormality of the heart[47].

The main terminology used to describe heart failure is based on measurement of left ventricular ejection fraction (EF). In patients with reduced contraction and emptying of the left ventricle (i.e. systolic dysfunction), stroke volume is maintained by an increase in end-diastolic volume (because the left ventricle dilates), i.e. the heart ejects a smaller fraction of a larger volume. The more severe the systolic dysfunction, the more the EF is reduced from normal and, generally, the greater the end-diastolic and end-systolic volumes. The major trials in patients with heart failure, mainly enrolled patients with an EF >35%, and it is only in these patients that effective therapies have been demonstrated to date. More recently, another group of heart failure patients have been described; those with an EF of between 40–45% and no other causal cardiac abnormality. Some of these patients do not have an entirely normal EF (generally considered to be >50%) but also do not have a major reduction in systolic function either. Because of this, the term heart failure with 'preserved' EF (HF-PEF) was coined to describe these patients. Most have evidence of diastolic dysfunction which is generally accepted as the likely cause of heart failure in these patients (hence the term 'diastolic heart failure'). However, more sensitive measures of systolic function may show abnormalities in patients with a preserved or even normal EF hence the preference for stating preserved or reduced EF over preserved or reduced 'systolic function'[47].

Heart failure is a common condition with a prevalence of 1 to 2% in the developed world and increasing to greater than 10% in elderly cohorts[48, 49]. During 2000-1, there were 84,151 admissions for people with heart failure in the UK[50]. This had risen to 141,566 UK admissions in 2009[51]. This is estimated to represent 2% of all NHS inpatient bed-days and 5% of all emergency medical admissions to hospital. Hospital admissions due to heart failure are projected to rise by 50% over the next 25 years largely due to the ageing population. It is estimated that the total annual cost of heart failure to the NHS is around 2% of the total NHS budget: approximately 70% of this total is due to the costs of hospitalisation[27]. The mean

number of admissions in the last six months of life for patients with heart failure is two, but there is wide variation. In the last month of life there are between zero and 20 admissions with a mean of 0.5[52].

Prognosis due to heart failure is poor. The five year prognosis is worse than that for many cancers[53]. There have been improvements in mortality due to improved medical management. Implantable cardioverter-defibrillator (ICD) placement reduces the risk of sudden death and as its use becomes more common, more patients will develop progressive advanced heart failure[54].

However, prognosis remains grave and data from a Canadian study assessing prognosis of patients newly admitted with heart failure still showed a 5-year mortality of 68.7% (median survival 2.4 years) and in those with an ejection fraction of less than 30% there was a median survival of only 3 months for those with a very high risk Enhanced Feedback for Effective Cardiac Treatment-Heart Failure (EFFECT-HF) score (prediction score to stratify the risk of death in heart failure patients)[55].

1.5 Summary of key literature regarding palliative care in advanced heart failure

Many of the key studies in this field are qualitative research, mostly semi-structured interviews or focus groups with patients, their carers or healthcare professionals.

A recent systematic review of the literature studied end of life conversations between patients with heart failure and healthcare professionals[23]. Barclay and co - workers used a "weight of evidence" framework which includes an overall assessment of the studies contribution in answering the review question. Data synthesis extracting data from the results section of each relevant paper and using narrative synthesis to explore new themes from the data were used[23]. Twenty three relevant papers were found, thirteen report information from patients; six from health professionals and four from both groups. The uniform view of patients was that end of life care conversations rarely took place if at all. The authors of the review noted that two papers from health care professionals (HCPs) did report end of life care conversations taking place[56, 57], one on a frequent basis[57]. The conclusion of the authors of the review about these papers was that there was discrepancy

between clinicians' and patients' reports of whether end of life care conversations have taken place at all and the amount of information given by clinicians. However, an alternative explanation is that these are different groups of patients in different services and so they could have had different experiences. The paper where the end of life care conversations were reported as taking place frequently was a retrospective case note review of joint palliative care cardiology services (two separate services), where there was close joint working and support between the two professional groups; none of the patients interviewed in the 21 other papers reviewed were identified as having a palliative approach to their care. The authors of the review also state that the level of evidence was low for these two studies and that further research was needed to explore this difference. These findings seem less contentious. The overall conclusion of the review was that end of life conversations rarely took place (both patient and clinician studies). Some patients would welcome such conversations, but many do not realise the seriousness of their condition or do not wish to discuss end-of-life issues. Clinicians are unsure how to discuss the uncertain prognosis and risk of sudden death; fearing causing premature alarm and destroying hope, and they prefer to wait for cues from patients before raising end of life issues. Consequently, the conversations rarely take place. The systematic review also discusses other barriers to end of life conversations which will be discussed later in the chapter.

Another systematic review from the perspective of social work reviewed the literature regarding the lived experience of heart failure[58]. It was less rigorous in its methods and explanation of its synthesis than the Barclay review. It identified 15 studies, 10 of which were interview studies with people who had heart failure, 2 were mixed methods (interviews and survey) and 3 were clinical case studies. Clinical case studies would not have the same methodological credibility as other qualitative research and some of the studies were used more as teaching tool than a research study. One study is presented in three different papers[59-61]. There is overlap between studies in both this review and the earlier Barclay review[59, 62-64]. These studies show an overwhelming sense of unmet need, often with a comparison directly, or through the literature of symptom burden comparable to that of patients with advanced cancer. In one of the studies, by Brannstrom and colleagues, the patients were enrolled in an advanced palliative home care team in

Sweden. Only four patients were interviewed, reflecting the small number of heart failure patients in the programme. The conclusion of the study, by the authors was that patients were on a symbolic "roller coaster" with the ups and downs of their illness but the palliative care home team nurses offered security and positive dependency by monitoring and being available, allowing them to remain at home and manage the ups and downs of the illness[65]. Clearly, this is a very small study, in one centre, but as with the retrospective case notes review it hints that the experiences of patients with advanced heart failure recognised and receiving palliative care is different from those receiving usual care.

An international literature review of the perspective of recipients and health professionals regarding palliative care in advanced heart failure demonstrated similar themes to the previous two reviews. Despite the title of the review referring to palliative care none of the heart failure patients were identified as having a palliative approach to their care[66].

A further search of the literature found no other studies of heart failure patient's experiences or perspectives (service evaluations are discussed in **section 1.6.1**) among those receiving any form of palliative care, either by generalist or specialists, although one paper did describe a planned study[67]. So apart from a small qualitative study[65], none of the patients interviewed in the literature about their experiences or perspectives of living with advanced heart failure were recognised as having or receiving any form of palliative care or a palliative approach to their care. This is a significant gap in the literature and the discussions below of barriers and facilitators of a palliative care approach should be read with that in mind, this perspective is missing. The finding of Barclay and colleagues' systematic review[23] that some patients do not wish to discuss their prognosis may be true, but it may also be that they have not had the opportunity. As discussed in **section 1.2,** this represents a model of care that was prevalent in cancer care decades ago. Current recommended communication strategies in cancer emphasise that although "truth hurts, deceit may well hurt more"[68 (p. 297)].

1.6 Comparison of heart failure and cancer palliative care

In the following section there will be a description of palliative care in advanced disease, specifically heart failure patients and a comparison with palliative care for

cancer patients. The impacts and barriers and facilitators of a palliative care approach will be discussed. The section will conclude with facilitators to a palliative care approach in heart failure and discuss any gaps in the evidence.

1.6.1 **Effects of palliative care in advanced disease**

1.6.1.1 General effects

The success of palliative care, particularly in cancer, is considerable and the UK is currently world leader in end of life care across the world. "End-of-life care" in this international evaluation by the Economist Intelligence Unit included palliative care (as defined by the WHO) but also referred to broader social, legal and spiritual elements of care relevant to quality of death[69]. There is good evidence of the benefits of palliative care for cancer patients in improving quality of care at the end of life and improving pain and symptom control and supporting carers. Palliative care may also improve home death rates and there is evidence to suggests that outcomes are better if palliative care is incorporated earlier in the disease trajectory[70-75]. For heart failure the effects of a palliative approach to care could be considerable. Heart failure remains a highly prevalent disease and despite significant improvements in management, many will live to develop end stage disease due to progressive heart failure. As discussed in **section 1.5** there is significant literature describing the burden of disease, poor quality of life and unmet needs of patients and their families living with advanced heart failure. Palliative care has the potential to improve communication not only between doctors and clinicians, in line with patient preference, but within families, reducing isolation and distress that occurs when "the elephant in the room" is not discussed[23, 58, 66].

An important aspect of palliative care is that it allows patient and carer involvement in decision making about their care in advanced disease. This can be through formal advance care planning or simply thinking about future care needs. Advance care planning is defined as:

> The process of discussing the type of treatment and care that a patient would or would not wish to receive in the event that they lose capacity to decide or are unable to express a preference….[41]

There is an increasing evidence base that advance care planning is important to many patients and leads to improved outcomes such as increased likelihood of end

of life wishes being carried out and improved quality of care for both patients and their carers[76-79]. However, there is little evidence that advance care planning is occurring for patients with heart failure[80], despite interest in this area from the cardiology community[81]. One aspect of advance care planning is decision making regarding preferred place of care, measured by congruence between preferred and actual place of death. A recent review has shown that a non-cancer diagnosis was found to significantly increase the incidence of incongruence and this disparity appears to have increased since 2004[82]. In the UK in 2010, 57% of cardiovascular (all types of cardiovascular disease) deaths compared with 41% of cancer deaths occurred in hospital. Between 2004 and 2011 only 0.3% of all cardiovascular disease deaths occurred in a hospice[52]. In 2011-12, heart failure patients made up only 1.3% of hospice inpatients, 2.2% of day patients, 0.6% of outpatients, 2.2% of hospital teams, 2.1% of hospice at home teams, 1.2% home care teams, 1.5% of combined homecare and hospice at home teams. Cancer patients made up between 72.4% and 87.3% of these services, demonstrating the inequality between access to specialist palliative care services for heart failure patients compared with cancer patients. This actually represents a four-fold increase in non- cancer diagnoses since 1999/2000[83].

Planning care in advance is particularly important for heart failure patients with an implantable cardioverter-defibrillator (ICD). If these are not re-programmed to pacemaker mode only, the dying process may be complicated by repeated shocks[84]. The American Academy of Hospice and Palliative medicine has highlighted this issue as one of the top five areas for change in the specialty[85].

Recognition of palliative care has important financial benefits for patients. In the UK, a patient with a prognosis of months, regardless of diagnosis has fast track access to certain benefits if the appropriate form (DS1500) is completed by their clinician. A retrospective case note review of patients who had died in one primary care practice demonstrated that no heart failure patients had the DS1500 completed compared with 33% cancer patients[86].

UK government policy implies that improving patients' preferences for home death will reduce hospital admissions and be at least cost neutral or even produce savings[32, 36]. The end of life care strategy acknowledges that it is difficult or even

impossible to calculate the cost of end of life care[32], although pilots are being planned[38]. The palliative care funding review, discussed **in section 1.3** suggests that improved recognition of palliative care needs, as well as optimised provision of services outside the hospital setting, could potentially reduce hospital costs with a saving of £180m per annum[38]. Internationally, end of life healthcare costs are escalating due to the aging population and hospitalisations at the end of life. However, palliative care has been shown to reduce the rate of hospital admissions and reduce healthcare costs[24, 87-92]. Another important cost is that of informal or family carers, who are mentioned in **section 1.2** and also provide palliative care. Indeed it is estimated that in the UK 500 000 people provide informal care for patients at the end of life, with an economic cost greater than the current health and social care budget, if this was to be provided by professional carers[93]. A palliative care approach recognises and provides support to these carers.

1.6.1.2 Evidence for joint working/specific models of care in advanced heart failure

Advanced heart failure is a complex condition and as stated in **section 1.2** an integrated/shared care model of palliative care in advanced heart failure is recommended in national and international guidelines[6, 7]. One reason is that optimised disease specific management is appropriate for symptom control and shared care allows disease specific management along with palliative care. An additional benefit is mutual education between teams such as cardiology, palliative care and primary care. Integrated models addresses concerns about palliative care services being overwhelmed as specialist palliative care only become involved with difficult or complex problems. An integrated model reduces the problems of an "all or none" approach which due to difficulties with prognostication mean that palliative care is not considered at all or very late in advanced heart failure. A key worker, such as GP or specialist nurse, may help overcome some of the difficulties of poor coordination and lack of clarity regarding roles. Takeda and colleagues reviewed organisation of clinical services for chronic heart failure. No palliative care services or palliative approaches to care were included, although two RCTs considered multidisciplinary approaches to care which reduced both advanced heart failure -related and all-cause readmissions[94]. The evidence for integrated cardiology and palliative care services is largely based on individual service evaluations[95-101], but includes only one RCT[102]. Nevertheless, the benefits of an integrated service with

respect to improvement in advanced care planning and reduction in hospital admissions have been demonstrated. A further three RCTs comparing integrated palliative care with usual care are on-going (trial identifiers: NCT01589601; NCT01519479 and NCT01304381). All of these trials have quality of life as the primary outcome, but with a variety of secondary outcomes and compare palliative care with usual care. Two of the trials are in the US and identify hospital patients and the intervention is palliative care consultations while in hospital. The third is a Swedish study investigating palliative home care. They have a variety of inclusion and exclusion criteria. These studies are welcomed as a significant addition to the evidence base towards exploring if palliative care is effective in advanced heart failure. The studies will not, however, answer the question of which patients should be referred and how to identify heart failure with palliative care needs as patient are randomly allocated. Another on-going study which aims to identify palliative care needs prospectively over time in a cohort of patients admitted due to heart failure may help to identify patient characteristics associated with a high burden of need[103]. In addition, a needs assessment tool which aims to help clinicians identify and triage unmet palliative care needs in those with progressive disease, has been adapted and validated for use in people with heart failure, but has not been tested in clinical practice yet[104].

In the UK patients with advanced heart failure are mostly cared for in the community by their GP[105]. As discussed in **section 1.3** tools such as the GSF, preferred priorities for care and the Liverpool Care Pathway can be used. These tools can be used for both cancer and non-cancer patients although there is limited evidence for the effectiveness in either patient group[106]. Heart Failure Nurse Specialists (HFNS) can provide a link between primary and secondary (cardiology) care, although they have evolved different roles in different areas[107]. An English national survey found that the overwhelming majority of HFNS considered that they had a role in providing general palliative care for their patients, and they were also important in liaison with specialist palliative care services[107]. In two regions, with support and training from specialist palliative care they provide palliative care and have discussions about advance care planning including preferred place of death. This has led to major improvements in rates of preferred place of death for patients

with heart failure. One of the regions is one of the recruiting centers for the qualitative study see **chapter five** and **six** and **7[57].**

Another model is proposed by Boyd and colleagues[108]. The Supportive and Palliative Care Indicators Tool (SPICT) act as a trigger for full assessment, including palliative care needs. It has been developed using a literature review and peer review. The website, to date, does not demonstrate any evidence beyond "good practice point" level of evidence, which was a consensus from the research group and invited peer review[109]. The SPICT is similar to the GSF prognostic indicator guide (see **figure 4**) and a team in Catalonia have adapted these tools for use in their setting[110]. None of these tools have been formally validated[110, 111]. A study comparing the Seattle Heart Failure model and the GSF prognostic indicator guide will be discussed further in **chapter three**[112].

1.6.1.3 Transition to palliative care

The majority of work in this area is with cancer patients. A review of the literature in 2006 led to the development of evidence based guidelines regarding conversations about transition to palliative care[113]. A recent systematic literature review looking at UK healthcare found only 12 studies[5]. The majority of these studies involved cancer patients and in only two studies was the transition the main focus of the study[5]. It concluded that there was little evidence regarding all aspects of the transition from active or curative care, to care incorporating a palliative approach but it was noted that it is often a distressing and unsettling period for patients and their families[5]. It also proposed the three main approaches described in **section 1.2**. The fact it is potentially an unsettling time is noteworthy. Often palliative care is accepted without consideration as a benign positive intervention, but as with all interventions, its effects both positive and negative should be explored.

Since this review, members of the systematic review of transitions team have undertaken a qualitative study, mostly focus groups, of healthcare professionals both in primary and secondary care regarding their view about transition to palliative care in acute hospitals. It has demonstrated that the transition to palliative care rarely takes place in the last year of life as recommended in government policy

and by the GMC. It recognises barriers to this taking place similar to those described below for heart failure[46].

1.6.2 **Barriers to palliative care in advanced disease**

1.6.2.1 Disease trajectory "prognostic paralysis"

Different disease trajectories have been described for cancer, single organ failure and general frailty[4]. These are important on a population level and for understanding the natural history of these diseases. However, there is much inter-patient variability and so it may be less helpful with the specific individual patient seen on the ward or in the clinic[114]. There is much uncertainty when dealing with prognostication at the end of life which has resulted in some clinicians feeling powerless and unable to act, described as prognostic paralysis[115]. Population level studies have described the heart failure trajectory as gradual decline, punctuated by episodes of acute deterioration, any of which may result in death or recovery. Death is described as seemingly sudden compared with the more predictable terminal phase seen with some cancers[4]. Treatments for various cancers provide several lines of intervention that may alter the natural history of the illness to a similar trajectory to a chronic illness interspersed by acute deteriorations. However in the field of oncology, in the UK at least, there appear to be fewer barriers to integrating palliative care according to patient need, even when prognosis is not clear. The NHS Cancer Improvement Programme promotes cancer service models based on individualised assessment, excellent communication skills and access to information throughout the cancer pathway. This is from diagnosis to living with and beyond cancer (survivorship). Palliative care is thus integrated within the cancer pathway, perhaps with intermittent episodes where palliative care services are accessed in response to particular problems earlier in the disease, leading to increased involvement as the disease progresses[116].

1.6.2.2 Recognition of advanced disease

The disease course of heart failure is often one of a gradual deterioration interrupted by exacerbations that towards end-stage may have no precipitant. Intensive intervention may be needed, with a good response, returning the patient to their previous trajectory. As the disease worsens, exacerbations may become more frequent and less responsive to treatment, resulting in 'revolving door'

admissions[108, 117]. In addition, the patient may become less tolerant to maintenance treatment due to renal failure or hypotension[6, 7]. A retrospective review has demonstrated that patients with heart failure have symptom burden, measured by functional status for a longer period of time than cancer patients[118].

There are many prognostic tools and variables available both for heart failure and cancer. Heart failure prognostic tools were mentioned in **section 1.6.1** and will be discussed further in **chapter three.** For now it is important to recognise that they do have limitations and have not been extensively validated. Prognostication is difficult and prone to error and so often avoided by clinicians, or when attempted, prognosis is over-estimated[119]. A systematic review suggests that clinicians generally make the same errors in prognosis and by the same magnitude[119, 120]. Christakis challenged clinicians to prognosticate about each patient they manage, and audit their practice. There is a risk that modern medicine has become obsessed with diagnosis and therapy resulting in prognosis being a neglected area of medicine lacking in research and teaching[119].

The SUPPORT study, a multi centred RCT of nearly five thousand seriously ill hospital patients demonstrated that by failing to act on prognostic information, patients continued to receive futile treatment, and experienced poor quality of life and care at the end of life. Not only do clinicians require prognostic information but the judgement and courage to use it appropriately[121].

1.6.2.3 Communication with patients

Recognition of advanced disease is only the first step in improving patient care. This needs to be sensitively and appropriately communicated to patients and their families. In the SUPPORT study, even when clinicians were given detailed accurate information about their prognosis, many failed to recognise and act on that information, and only 15% discussed it with the patients and or their families[119, 121]. The Barclay systematic review of literature concerning conversations about end of life care between patients with heart failure and healthcare professionals, discussed in **section 1.5,** suggests that clinicians wait for cues from patients before raising end of life issues, while patients commonly wait for clinicians to raise these issues: as a result, the conversations rarely take place[23]. Interviews with 106 hospitalised patients with heart failure across five tertiary centres in Canada confirmed that

patients valued honest communication by the doctor as amongst the most important issues in relation to end of life care[122]. These views are reflected in a large study of 2331 cancer patients, 1046 of whom were being treated palliatively, 87% wanted all possible information, good or bad, including a similar proportion in the palliative group[123]. In cancer palliative care significant strides have been made with training in communication skills[124]. Truth telling tailored to an individual's requirements, whilst maintaining realistic hope is a skill, and although it is difficult, it is usually the best way to work together to plan future appropriate management, and does not destroy hope, a fear expressed by clinicians[68]. Factors that maintain hope in the terminally ill include:

- Feeling valued as a person (reminiscence)
- Meaningful relationship (humour)
- Realistic goals
- Pain and symptom relief[125]

Cardiologists in a focus group study confirmed that they rarely raised end of life issues with patients, citing lack of confidence and training in discussing end of life issues as a significant barrier. It also takes time, and may require restructuring of services, for example out-patient cardiology clinics[56]. Disease specific communication guidelines for cardiology have very recently been produced and will enable patients, if they wish, to discuss their poor prognosis and be involved in decisions about their future care despite uncertain disease trajectories by[81] "hoping for the best, and preparing for the worst"[126] (p. 439).

1.6.2.4 Societal and professional lack of understanding of diagnosis and needs

There is a risk that clinicians as well as patients feel the symptoms in heart failure are inevitable[127] and untreatable making a full assessment of palliative care needs less likely. It is known that patients and carers have a poor understanding of heart failure[128], the stage of their illness, its treatments and aims of treatments and the poor prognosis[21, 59, 61, 129, 130]. Patients report being given little information, or discussed in complex language difficult to understand and the term "heart failure" itself is perceived as a barrier by some clinicians[21]. In addition, if palliative care is only perceived as something that is required only for the imminently dying or for

cancer patients this can be a significant barrier. Clinicians find it difficult for many reasons to recognise that a patient is approaching the end of their life. There are societal norms with the avoidance of death and professional codes such as the duty of the doctor to preserve life and may result in clinicians seeing death as a failure. Increased therapeutic options may make it tempting for clinicians to strive for any prolongation of life, even if this is futile, or merely prolongs the dying itself.

1.6.2.5 Fragmentation of care

Many different disciplines are involved in patients with advanced heart failure: cardiology, general medicine, care of the elderly, emergency medicine and primary care and palliative care across community, hospital and hospice settings. A qualitative study by Hanratty and collegues in 2002 demonstrated poor coordination of services between hospital and community, lack of clarity regarding different speciality clinicians' roles and the need for improved communication between all the professionals involved in patients with heart failure and palliative care needs[56].

Many patients would prefer to remain at home, especially at the end of life, and see their GPs as the most important person coordinating their care[56]. A role that GPs are generally able and willing to undertake, but for heart failure it has been suggested they would like education regarding heart failure management and communication issues[131]. Cardiologists lack experience in palliative care[56, 132]. Palliative care specialists also require education, for example, regarding medications and cardiac devices. This is important as there is a need to continue some disease modifying medications for patients with heart failure to control symptoms[8], [132]. Some palliative care specialists have also expressed concern that scarce resources will be overwhelmed[3] although established integrated services have not reported this to be the case[97, 133]. Cancer palliative care services tend to be better developed. As a large number of professionals are involved in heart failure care it can make it difficult to understand who is responsible for initiating discussions about end of life care. Because of the barriers to communication already discussed it could mean that each professional leaves it to someone else meaning it never happens.

An important area with regard to fragmentation of care is out of hours care. In cancer palliative care there are already concerns about poor coordination in out of

hours care[134-136]. In the UK out of hours GPs are a separate service and in order to facilitate good out of hours palliative care, generally a specific communication or handover is required. Advanced heart failure because of difficulty of recognising advanced disease may mean this handover is less likely to happen creating another barrier to effective palliative care for heart failure patients.

1.6.3 Facilitators to a palliative care approach in heart failure and gaps in the evidence

An important facilitator to a palliative care approach in heart failure is the current policy drive in the UK towards palliative care for heart failure patients. In conjunction with the significant progress and lessons learnt from palliative care for cancer patients over the last half century. It is also a highly prevalent disease with a poor prognosis and significant unmet need as shown by many different qualitative studies.

Gaps in the evidence include that although the policies and guidance suggest that palliative care should be introduced in the last year of life, there is no or very limited evidence for how that period can be identified in advanced heart failure **(figure 4).** The documents also define "identification" as the first stage in any end of life or palliative care pathway (**figure 5**). Integrated models with triggers for assessment, equally have limited evidence for the triggers[108, 110, 111]. There is lack of clarity as to why the last year of life been chosen as the time for introducing palliative care as it appears to be an arbitrary period of time. In addition, the disease trajectory for heart failure may be longer than that for cancer with an extended period of symptom burden, beyond one year[118]. Evidence in cancer suggests that earlier integration of palliative care is beneficial[71] and so it may be that earlier palliative care should be recommended. The qualitative studies compare advanced heart failure with cancer and demonstrate inequalities and unmet need. Inequalities have been demonstrated with regard to access to specialist palliative care. A quantification of the recognition of the need for a palliative care particularly in primary care has not been undertaken. There has been an unquestioning acceptance that the cancer palliative care model should be used for advanced heart and there has been only limited investigation of how models of care for advanced heart failure will work in practice or how patients will be identified for these models of care. The qualitative studies of patents, carers and healthcare

professionals' experience of care for patients with advanced heart failure did not include any significant number of patients with heart failure who were also recognised as needing or receiving any form of palliative care and so we do not know if the experiences or perceptions would be different in this group.

1.7 Summary

A definition of palliative care encompasses a palliative care approach by generalists in primary and secondary care and access to specialists for whom palliative care is their "core business". For both specialist and generalist palliative care the patient and their family are at the centre of decision making. Open communication and proactive care are also important components of palliative care. There are three ways of defining transition in palliative care: a shared transition point, a phased transition and a simultaneous care approach; the latter has been recommended in heart failure. UK policy recommends a palliative care approach for patients with heart failure and access to specialist palliative care services as required. However, patients cannot take the first step on this path unless they have been identified by prognosis, that is, as being in the last year of life. This relies on clinically useful prognostication, which will be explored in **chapter three**. Only then other steps such as communication, assessment and proactive planning can be taken. Current knowledge with regard to palliative care for patients with heart failure and identified gaps in this knowledge are defined in **figure 6**. These gaps will be used to define the research question in **chapter two**.

Current knowledge:

- UK health care policy, in the last ten to fifteen years, has emphasised palliative care for patients with heart failure (**section 1.3**)
- Policy documents define "end of life" as the last year of a patient's life (**figure 4**)
- Heart failure has an uncertain disease trajectory with periods of deterioration, stability, and improvement in an unpredictable manner (**section 1.6.2.1**)
- Patients with heart failure experience a significant burden of supportive and palliative care needs which may be experienced for longer than the last year of life (**section 1.5, 1.6.1.1 and 1.6.2.2**)
- HCPs find it difficult to identify the palliative population in heart failure (**section 1.6.2.1 and 1.6.2.2)**
- HCPs are reluctant to discuss a palliative approach for patients with heart failure for among other reasons, fear about destroying patient's hope (**section 1.6.2.3**)
- Therefore, the "end of life" framed as the last year is likely to be unfit for purpose
- Policy documents recommend access to both a palliative care approach and to specialist palliative care services for heart failure patients at the end of life (**section 1.3**)
- Both quantitative and qualitative evidence indicates significant inequity of access to generalist and specialist palliative care services (**section 1.6.1.1)**

Gaps in knowledge:

1. How to identify the palliative population in heart failure?
    - Prognosis (last year of life)
    - Problem based?
    - Other
2. Palliative population in heart failure in primary care?
    - Is it recognised?
    - Is there inequity in recognition of the palliative care population in primary care between cancer and heart failure?
3. What are the effects of a palliative care approach for people with advanced heart failure and their families?

Figure 6. Summary of current knowledge and gaps in knowledge

2 Defining the research questions for the thesis

2.1 Introduction

Chapter one identified gaps in the current research literature regarding palliative care for patients with heart failure (**figure 6).** This chapter will develop discrete research questions arising from this process. The methodology for each research question will be summarised in this chapter and described in more details in chapter three, four and five.

2.2 Overarching research aim

The overarching aim of the thesis is to explore a palliative approach to care for community based patients with advanced heart failure with regard to the following: recognition of need, transitions in care and impact on patients, carers and clinicians.

In order to achieve this aim a mixed method study will be used, with both qualitative and quantitative research methods. The mixed method approach is mostly parallel, in that the studies will be conducted separately and simultaneously, with integration of the findings, rather than the studies being conducted consecutively and the findings used to influence the design of the next study. This will be discussed further in **chapter eight**.

Details of the three methods used to answer this question are:

1. Systematic literature review of prognostic markers associated with the last year of life
2. Quantitative analysis of data from contemporaneously collected GP electronic medical records
3. Qualitative interview study with patients, carers and health care professionals

2.3 Systematic literature review of markers of advanced heart failure

Models of care and current policy make presumptions that there are markers of advanced disease which could trigger a palliative care assessment[108, 109] or identify someone as in the last year of life **(figure 4)**. Policies also define "identification" as

the first stage in any end of life or palliative care pathway **(figure 5).** As the systematic review by Van Mechelen showed- there is no easily defined palliative care population[9]. Identification can be by prognosis, by need or by other means. The first stage of the research will therefore be a systematic review of variables that have been studied with regard to relationship to survival to see if any are associated with being in the last year of life in advanced heart failure. If present, these may help in the identification of the last year of life in heart failure patients.

The systematic literature review question: what prognostic markers are associated with being in the last year of life in adult patients with heart failure?

2.4 Analysis of contemporaneously collected GP records from a national database: general practice research database (GPRD)[1]

The next part of the thesis will investigate and quantify the suggested inequity between heart failure patients and cancers patients regarding recognition of the need for a palliative care approach. The qualitative studies discussed in **section 1.5** have demonstrated a high level of unmet need; they used small samples but generated a large amount of rich data and indicate that, compared with cancer patients, the need for a palliative care approach is rarely recognised in practice. A small quantitative audit from one GP surgery highlighted gross inequality with only one heart failure patient (4%) being on the palliative care register compared with 33(61%) of cancer patients. This was despite there being evidence of poor prognosis in both groups[86].

This study will use general practice research database (GPRD), a national collection of anonymous computerised patient records from selected GP practices, allowing quantification of the suspected inequality on a large national database, which is representative of all GP practices in the UK. Practice based cancer and heart failure registers will identify the population of interest. Patient inclusion on the palliative care register will be taken as a marker for recognition of the need for a palliative care approach.

[1] GPRD is now known as Clinical Practice Research Data-link (CPRD)

2.5 Qualitative study: perceptions of patients, carers and health care professionals regarding the transition to a palliative care approach on advanced heart failure

The literature to date, mainly consisting of qualitative research has focused on any patient with advanced heart failure, usually identifying unmet palliative care needs and that a palliative care approach would be appropriate but has not been recognised. The literature has explored some of the barriers to a palliative care approach for heart failure patients and some of the difficulties that patients and their families with advanced heart failure experience[23, 58, 66].

This study will further explore understanding in this area by focusing on patients with heart failure where it *has* been recognised by their HCPs that a palliative approach to care would be appropriate. This means the student can explore the transition to a palliative care approach in more detail than previous studies, identifying how barriers to the palliative approach were overcome, what difficulties still remain and more importantly the consequence of this transition for the patient and their carers, both positive and negative.

The research question for the qualitative section of the thesis is: what are the perceptions of patients, their carers and HCPs regarding the transition to a palliative care approach in advanced heart failure?

2.6 Explanation regarding other parts of the research question

The question will be community focused as this is where patients are cared for the majority of the time. The scope is beyond primary care to the ***community*** to recognition that the community has a wider field and influence than primary care health and social services alone such as HFNS to include family, friends and neighbours.

Carers are defined by NICE in their 2004 document: palliative and supportive care as "lay people in a close supportive role who share in the illness experience of the patient and who undertake vital care work and emotion management"[137(p. 155)] . Other terms that may be used are family caregivers or informal carers to differentiate from professional carers. For this thesis carers can be family members or others who are in a close caring role with the patient such as friends or neighbours. Although described as lay people, they may concurrently have roles as

health care professionals (such as working as a nurse), but in this role they are caring as a family member or informal carer.

Chapter one demonstrated that many different definitions of palliative care and end of life care are used and so for the thesis the term a ***palliative approach to care*** will be used. The reason for this is that it keeps the definition broad and so does not exclude any care that could be seen as palliative care and is not time bound. It includes both generalist and specialist palliative care. It is an approach to care, rather than just about access to services. Furthermore, it avoids confusion about end of life care or defining prognosis for example only including patients in the last year of life.

Comparison with cancer is important because as discussed in the literature review in **chapter one** palliative care is often seen as synonymous with cancer care and so will be an aspect of the research, for example cancer patients are used as the comparator group in the GPRD study. For the qualitative study the student has decided not to use a comparator cancer group. Initially, it was a practical issue of time and resources. It is also important methodologically. The literature review has demonstrated that heart failure and cancer are very different diseases, have different trajectories, with different beginnings, for example often no firm date of diagnosis for heart failure compared with cancer. Simplistic comparisons may result in missing important differences. There has been criticism of the uncritical introduction of the cancer palliative care model to other life threatening illnesses[23]. Therefore, to avoid assumptions, the experiences of patients, carers and HCPs with heart failure only will be explored in this thesis.

This research is pragmatic in nature, stemming from the recognised gap in the research literature and a desire to make a difference to the care of patients with heart failure who have unmet palliative care needs. It should be taken in the context of UK health care and current UK healthcare policy. It is not driven by any specific theoretical framework.

2.7 Summary

The overarching aim of the thesis is to explore a palliative approach to care for community based patients with advanced heart failure: recognition of need,

transitions in care and impact on patients, carers and clinicians. A mixed methods study design has been chosen to include: a systematic literature review of prognostic variables (**chapter three**), a GP database study (**chapter four**) and a qualitative semi-structured interview study (**chapter five, six** and **seven**). The mixed method design is an integration of the findings of the three studies conducted in **chapter eight**.

A fundamental advantage of a mixed method design is that the findings of all three studies are integrated to achieve the aim of the thesis in more depth. This will be conducted in **chapter eight.**

3 Systematic literature review of prognostic variables associated with being in the last year of life in adult patients with heart failure

3.1 Introduction

Palliative care is recognised as important in advanced heart failure but is a complex area with no clear evidence for any specific model of care and has not yet been widely introduced. As was highlighted in **chapter one,** UK policy places prognosis (being in the last year of life) as the defining trigger before the patient can access a palliative care approach. This forms a primary barrier to palliative care for patients with heart failure and depends on the availability of clinically useful prognostic variables to assist the clinician to predict those who have reached this phase of heart failure. Therefore this chapter will report a systematic literature review to determine clinically useful prognostic variables associated with being in the last year of life in adult patients with heart failure.

3.2 Background

Palliative care for patients with heart failure is increasingly recognised as important[7, 95, 138]. However, it is a complex area with no clear evidence for any specific model or models of care and has not been widely introduced. Proposed models of care often recognise that the need for palliative care should be based on need rather than specific points in the disease trajectory but often include triggers/ markers of advanced disease/ clinical indicators considered to indicate "the last year of life" to prompt a clinician to consider a palliative care approach[40, 138, 139]. The evidence base for these markers is often not clear. Research into barriers for introducing palliative care often state the difficulty in predicting prognosis as a barrier to palliative care for patients with heart failure, and is complicated by a variable disease trajectory that includes the risk of apparent sudden death[4, 59].

Any clinically useful predictors in heart failure identified from the systematic literature review will not only have relevance in clinical practice, but will also be used to determine which, if any, of the identified markers will be useful for a GP database study comparing recognition of advanced disease and the palliative care approach for cancer patients and patients dying of advanced heart failure.

Systematic reviews of prognostic information are not as well developed as systematic reviews of clinical effectiveness. The Cochrane collaboration has a prognosis methods group which is currently developing prognosis systematic reviews methods[140]. It defines four key questions

1. What is the course of the condition / disease? (Descriptive)
2. What prognostic variables are associated with outcome? (Explanatory)
3. What groups of prognostic variables best predict outcome? (Outcome prediction)
4. What are the interactions between intervention and prognostic variables?

This review will focus mainly on question 2, but also question 3 if relevant papers are available.

The review question is; what prognostic variables are associated with being in the last year of life in adult patients with heart failure?

3.3 Review objectives

3.3.1 Primary objectives

To determine prognostic variables associated with being in the last year of life in adult patients with heart failure (question 2).

3.3.2 Secondary objectives

To determine which variables could be used in a GP database study

To determine which variables best predict being within the last year of life (question 3).

3.4 Methods

This method follows the structure of the Cochrane collaboration for systematic reviews of the effectiveness of interventions, but has been adapted, where appropriate, for review of prognostic variables.

3.4.1 **Criteria for selecting studies for this review:**

3.4.1.1 Types of studies / Design

All randomised or quasi-randomised (blinded and non-blinded) controlled trial including cluster and cross over trials

Cohort studies (prospective and retrospective)

3.4.1.2 Types of participants

All patients over 18 years with a diagnosis of heart failure including with 'preserved' ejection fraction (diastolic heart failure)

Populations where all participants comprised a particular sub-population of people with heart failure, eg. only patients with cardiomyopathy, only patients who were post-transplant or only patients with an implanted cardiac device, were excluded.

3.4.2 **Type of prognostic variables**

Any prognostic variable, for example clinical event, demographic data, laboratory result were considered.

Studies that investigated prognostic markers that are not routinely available in clinical practice were excluded.

All studies were assessed for risk of bias using the Hayden score (described in **section 3.4.5**) and only studies that were at a low risk of bias were included. All texts with a score greater than or equal to nine were included in the final review.

The comparison and intervention groups are less relevant to prognostic studies (than effectiveness systematic reviews) and is often not present (for example cohort studies).

For selected randomised or quasi-experimental studies, the comparison group could include any stated alternative which constituted a control group. Examples are:

"Usual Care";

"Placebo";

"No intervention",

"Control group"

If an intervention group is present consideration is required for randomised studies with regard to the effect of an intervention on survival. Therefore, for randomised studies when the intervention had *no effect* on survival (relative risk=1.0), the intervention and comparison group could simply be combined to study baseline prognosis. If the intervention did have an effect on survival the groups were still combined, but the treatment variable was then included as a separate predictor in the multivariable model. In this review interventions are studied on their independent predictive effect and not on their therapeutic or preventive effects.

3.4.3 **Types of outcome measures**

The following outcome measures were used.

3.4.3.1 Primary

Death from any cause

3.4.3.2 Secondary

Cardiac death

Transition to palliative care approach

Heart transplant

3.4.4 **Search strategy**

The following databases were searched, current at 5 October 2011:

Cochrane Library

COCHRANE DATABASE OF SYSTEMATIC REVIEWS Issue 10 of 12, Oct 2011
COCHRANE CENTRAL REGISTER OF CONTROLLED TRIALS (CENTRAL) Issue 4 of 4, Oct 2011
Other Reviews (DARE) Issue 4 of 4, Oct 2011
Methods Studies Issue 4 of 4, Oct 2011
Technology Assessments Issue 4 of 4 Oct 2011
Economic Evaluations Issue 4 of 4, Oct 2011

Ovid MEDLINE(R) 1948 to September Week 3 2011

Embase 1974 to 2011 October 04

EBSCO CINAHL (1982 to 2011)

BNI (1994 to 2011)

AMED (Allied and Complementary Medicine) 1985 to September 2011, searched 5 October 2011

Web of knowledge (incl Science citation Index and ISI Proceedings) to search for conference proceedings searched 4 October 2011

Index to thesis www.theses.com

Current Controlled Trials (clinical trials register)

International clinical trials registry platform, WHO (clinical trials register)

The search terms were developed in conjunction with Ms Catriona Kemp, Hull York Medical School, Librarian. The search terms reflected two aspects of the question:

Population: heart failure patients in the last year of life /advanced /palliative

Prognostic variable: Prognosis studies or markers

Used both free text and thesaurus matching and UK and US spelling for all searching and there were no limitations, for example included all possible years and languages.

Figure 7 shows the search strategy and **appendix one** shows the search string for searching in Ovid MEDLINE. This search was adapted to use in the other databases.

	Search area	Terms with Boolean operator	Dates for database	Medline hits
A	Heart Failure	heart failure OR ventricular function OR cardiac failure OR ventricular dysfunction OR ventricular systolic dysfunction OR cardiac dysfunction OR cardiac function OR cardiac overload OR systolic dysfunction OR myocard* dysfunction OR cardiac insufficiency OR heart insufficiency OR CHF	1948 to September Week 3 2011	204 085

		OR CCF OR HF OR LVSD.		
B	End of life /advanced /palliative	palliative care OR terminal care OR hospice care OR end stage OR late stage OR dying OR end of life OR terminal* ill OR advanced disease advanced cancer OR advanced illness OR palliat* OR advance* directive*		173 210
C	Prognostic studies	cohort studies OR incidence OR Mortality OR follow-up studies OR prognos* OR predict* OR course		3 081 736
D	Prognostic markers	marker* OR trigger* OR clinical indicator* OR Estim* survival OR Risk score*		700 445
Limits	Remove duplicates			
Strategy	Search 1: A Search 2: B Search 3: C Search 4: D Search 5: A and B			5 953
	Search 6: C or D Search 7: Search 5 and Search 6			3 585 480
	Searches 7 will have titles and abstracts assessed for retrieval of papers			3 138

Figure 7. Search terms for the systematic review

In addition: the reference lists of all included studies and key review articles were hand searched.

The search terms were not limited to English, however, there were insufficient funds available for translation of all non-English texts, therefore it was limited to the expertise available within the research team which are French, Spanish and Japanese, other languages were excluded.

3.4.5 **Data collection and analysis**

3.4.5.1 Study selection

Two reviewers were involved in all stages of study selection. This was the student and her two supervisors who shared the second reviewing role. The reviews were completed independently, followed by a meeting for discussion where a final decision was made by consensus, between all three, if necessary.

Results of all the searches were collated using Endnote version 4 reference management software and duplicate reports deleted.

Titles and abstracts were reviewed to exclude any obviously irrelevant reports using criteria for study selection at abstract stage (**appendix two**) to guide decision making. A full text copy was obtained for all reports that were included, or had insufficient information for exclusion at this stage.

A study eligibility form was used and piloted on the first three studies to examine full test reports for compliance with eligibility criteria. No changes were needed as a result of this pilot (see **appendix three**).

Multiple reports from the same study were identified and excluded.

The plan was to contact original authors if any further information was required to make decision, or in the event of missing key information such as missing data. However, it was not necessary to contact original authors.

As only studies at low risk of bias were to be included, two reviewers (the student and one supervisor, MJ) scored half the papers each and double reviewed a sample of 20, to ensure good agreement between the two reviewers. The specific exclusion criteria relating to studies that investigated prognostic variables *not routinely available in clinical practice* were all reviewed by both the student and MJ.

A flow diagram in accordance with the Preferred reporting items for systematic reviews and meta-analyse (PRISMA) statement[141] which records and summarises the decisions and processes in the selection of included studies can be seen in **Figure 8**.

Excluded studies were recorded in a table, in **appendix five** with reason(s) for exclusion.

3.4.5.2 Data extraction plans

Data from the included studies were added to a data extract form by the student. The data extraction tool (**appendix four**) included information, adapted from Table 7.3. of chapter 7 of Cochrane Handbook Checklist of items to consider in data collection or data extraction[142]. It was piloted on the first three papers; no changes were needed.

The aim was to extract raw absolute data as much as possible; that is, raw numbers rather than percentages or measure of effect. Each primary data set was only used once, even if there were serial or duplicate publications.

Where studies were only available as abstract stage, the plan was to contact authors for further information. However, due to the large number of conference studies it was decided that those that were subsequently available as full published papers would be excluded. If there was any other missing data or details it was planned to contact the authors for further information, however, this was not necessary, perhaps because only studies that were at low risk of bias were included.

3.4.5.3 Validity assessment/risk of bias assessment

Systematic reviews of prognostic studies are often limited by the poor standard of the original prognostic studies[143]. Hayden and colleagues have suggested six possible sources of biases in prognostic studies[144] and strongly recommend assessment of bias. They argue against using a "quality score" approach that assign points on the basis of the number of "positive" quality items because this reduces scientific judgment. Instead they suggest that reviewers thoughtfully consider overlapping methodological issues and the direction of the potential bias for each case. The Cochrane Handbook of Systematic Reviews of Intervention argues that the use of composite scales or weighting in the meta-analysis is misleading as these are arbitrary[145]. It was therefore planned to use all eligible studies in the report and to complete a risk of bias table to display information about the risk of bias in each study using the six domains suggested by Hayden and colleagues[144]. This is outlined in a table in **appendix four.** However, due to the large number of eligible studies a

scoring system was used to exclude studies at high risk of bias. A score was added to the Hayden risk of bias tool with yes =2, partly =1, no or unclear =0 with a possible score of between 0 to 12. A key strength of a well-conducted systematic review is the minimization of bias at the level of study inclusion, so that the overall synthesis accurately reflects all research undertaken in the field that is relevant to the research question[146]. However, the majority of the studies found in this review are not designed *a priori* to predict prognosis but rather as secondary analysis of data from other studies and so this principle is less relevant. Often the only conclusion of prognostic systematic reviews is a discussion about poor quality studies and the need for better quality studies[143, 147]. By excluding poor quality studies this review was able to go further that this general conclusion and be specific about what is required in future research. Studies were excluded in a clear and transparent procedure. The scoring system was not used to display risk of bias assessment in the included studies, it was just described, see **table 3**. Risk of bias assessment was undertaken by two reviewers (the student and one supervisor, MJ) and 20 papers were double scored. The tool was piloted on the first three studies and no changes were needed.

The original plan was to use sensitivity analysis to exclude studies at high risk of bias (e.g. scoring at high risk on more than four of the domains) from the analysis and examine the effects this had on the results. However, as all studies at high risk of bias were excluded in the final method because of the high number of studies retrieved, this was not possible.

3.4.5.4 Data analysis plans

The initial plan had been to extract summary data in order to calculate absolute risk estimates but this was not available for any of the studies. Alternatively hazard ratio (HR) e.g. for time to event data, relative risk ratio or odds ratio for the main outcome which is all-cause mortality and or the secondary outcomes cardiac death, referral for palliative care or receiving heart transplant were used. The statistical model used e.g. cox proportional hazards model, was also recorded. In order to combine the data from as many studies as possible, the assumption was made that for a relatively rare outcome, the relative risk or odds ratio approximates the hazard ratio (HR). Where available confidence intervals (CI) as

well as P values are presented and mean values are accompanied by standard deviation (SD).

Hazard is the proportion surviving by any given time, which is also the estimated probability of survival to that time for a member of the population from which the sample is drawn[148].

Odds are the ratio of the probability that the event of interest occurs to the probability that it does not. This is often estimated by the ratio of the number of times that the event of interest occurs to the number of times that it does not[149].

Risk describes the probability with which a health outcome (usually an adverse event) will occur[150].

Adjusting or controlling for a variable is defined as assessing the effect of one variable while accounting for the effect of another (confounding) variable. Adjustment for the other variable can be carried out by stratifying the analysis (especially if the variable is categorical) or by statistically estimating the relationship between the variable and the outcome and then subtracting out that effect to study which effects are left over. Adjustment results in adjusted variables such as adjusted odds ratios and adjusted hazard ratios etc[151].

The adjusted results were recorded. The reason for this is that the different groups, for example, those who died or survived have multiple confounding variables. Unlike with a trial unadjusted results cannot be used as the outcome might not be due to the measured marker but to other variables such as age or ejection fraction, that also affect mortality. It is interesting to know if a prognostic marker offers additional prognostic information over and above previously identified prognostic information, and so then to add it to known conventional risk factors in the model. For each primary adjusted variable the other prognostic variables that were in the model for control of the confounding, the covariates were also recorded. Often non-significant covariates were removed from the model and only values for significant covariates were recorded in the studies. Known prognostic variables should not be removed from the model to allow comparison with other reported studies. Comparison of models with and without

the primary prognostic variable can provide an estimate of its independent effect[147, 152, 153].

Descriptive synthesis was undertaken as most variables were only identified once or were adjusted using different variables in the regression models making meta-analysis unfeasible. The method for the meta-analysis if it is would have been possible is found in **appendix six**, where a summary of differences between the original and final review protocols is also provided.

3.5 Results

One hundred and eighty nine full-text articles were assessed for eligibility for inclusion in the systematic review. Three studies in French, Japanese and Spanish respectively were translated in sufficient detail to make a decision about their eligibility[154-156]. For six conference abstracts it was necessary to obtain full papers in order to make a decision about eligibility[112, 157-161].

The decisions about study selection are recorded on a PRISMA flow diagram, **figure 8**. Thirty two studies were included in the review.

Excluded studies are recorded in **appendix five**, with the reasons for exclusion.

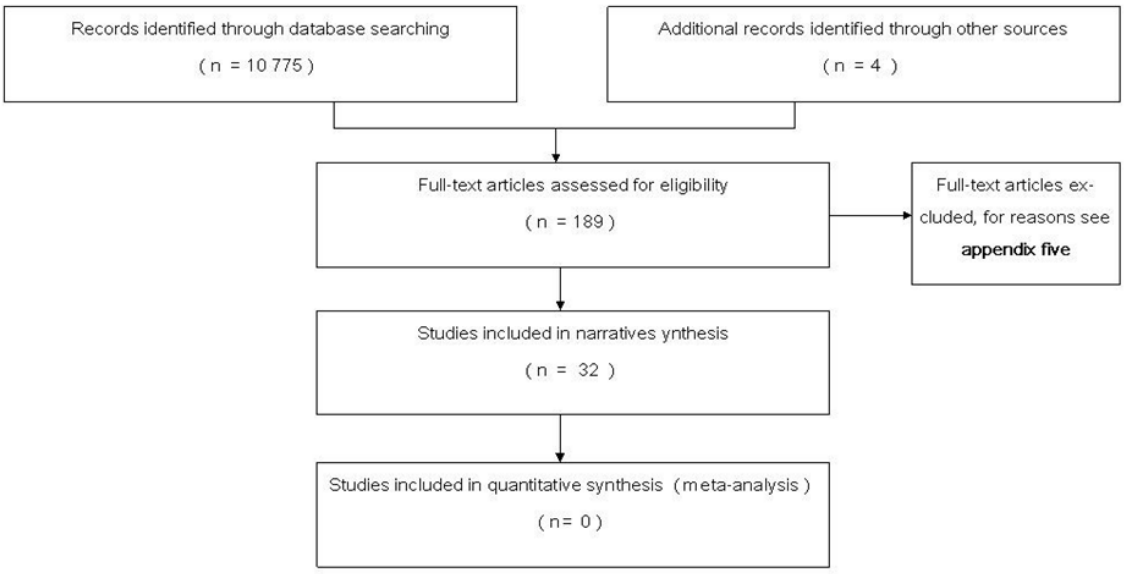

Figure 8. Improving the quality reports of meta-analyses or randomised controlled trials: the PRISMA statement flow diagram[141].

Single predictor studies exploring demographic variables are shown in **table 1**. These data indicate that hospitalisation and male gender are possible prognostic variables associated with being in the last year of life.

Table 1: Single predictor studies exploring demographic variables. If values are different to column heading they are detailed individually.

Study Number	Methods Study Type (if RCT intervention follows in brackets) Mean follow up (+/-SD) in years	Participants Total N= Setting Mean age (+/-SD) years Per cent male	Outcome measure	Primary prognostic variable	Other prognostic variables (covariates) for which the primary predictor variable is adjusted	Results expressed as HR (95% CI) and corresponding P-value and adjusted for variables in the previous column	Comment
1 Abrahamsson et al., 2009[162]	RCT CHARM (Candesartan V placebo) 3.3 (SD not stated)	7599 Multi centred international trial. Not stated if OPD or inpatient "Average age of 66" 68.4	All-cause mortality	Hospitalisation for acute coronary syndrome	Age LVEF Diabetes: (insulin-treated Diabetes or other) BMI Gender NYHA Smoking status Presence of cardiomegaly Prior HF hospitalisation Randomised treatment allocation	After first myocardial infarction 2.32 (1.69, 3.20); p<0.001 After first unstable angina 1.36 (1.04, 1.80); p<0.027 Both at 6 to 18 months after the event	HR calculated at time intervals (0–1, 2–7, 8–30 days, 31 days–6 months, 6–18 months, and 18+months) after the main predictor event ie hospitalisation for acute coronary syndrome. Hospitalisation was a statistically significant predictor but its effects reduced over time.

Table 1: Single predictor studies exploring demographic variables. If values are different to column heading they are detailed individually.							
Study Number	Methods Study Type (if RCT intervention follows in brackets) Mean follow up (+/-SD) in years	Participants Total N= Setting Mean age (+/-SD) years Per cent male	Outcome measure	Primary prognostic variable	Other prognostic variables (covariates) for which the primary predictor variable is adjusted	Results expressed as HR (95% CI) and corresponding P-value and adjusted for variables in the previous column	Comment
2 Adams Jr et al., 1999[163]	RCT FIRST STUDY (IV epoprostenol (flolan) V standard management for heart failure alone Mean follow up not stated	471 (430 in this analysis) Multi centred international trial. NYHA functional class IIIB or IV HF EF of <25% (or <30% if on an inotropic infusion) 64+/-10 years men, 64+/-11 years women 77	All-cause mortality	Male vs Female	6-minute walk Dobutamine use Mean Pulmonary Artery Pressure Age Epoprostenol use	2.18, (1.39, 3.41) P<0.001	Advanced heart failure population On ACE-Is, unless contraindicated Being male was a statistically significant predictor of death.
12 Chin & Goldman, 1998[164]	Prospective cohort (chart review) Mean follow up not stated	436 (435 one chart missing) Consecutively admitted non-elective patients with HF to US teaching hospital 31%≤60, 28% 61-70, 21% 71-80, 20%>80 47	All-cause mortality	Male vs Female	Planned to adjust for these variables as p≤0.1 in bivariate analysis Race CMIS Sodium	P=0.32 in bivariate analysis (log rank test) so not added to multi variable model	Not powered to detect difference in mortality by gender so unable to determine if there was a difference

Table 1: Single predictor studies exploring demographic variables. If values are different to column heading they are detailed individually.							
Study Number	Methods Study Type (if RCT intervention follows in brackets) Mean follow up (+/-SD) in years	Participants Total N= Setting Mean age (+/-SD) years Per cent male	Outcome measure	Primary prognostic variable	Other prognostic variables (covariates) for which the primary predictor variable is adjusted	Results expressed as HR (95% CI) and corresponding P-value and adjusted for variables in the previous column	Comment
32 Solomon et al., 2007[165]	RCT CHARM Candesartan v placebo) Median 38 months	7572 Multi centred international trial. Not stated if outpatient or inpatient Not clearly stated Not clearly stated	All cause-mortality	Non-fatal first hospitalisation for HF	Same as study 1	3.15 (2.83–3.50) p<0.001	NB Same as study 1 CHARM but different prognostic variable and analysis not calculated at time intervals Hospitalisation was a statistically significant predictor of death

Table 1. Summary of single predictor studies exploring demographic variables.

Key: RCT = randomised controlled trial; SD =standard deviation; CI = confidence intervals; HR = hazard ratio; OPD = out patient department; BMI = body mass index; NYHA = New York Heart Association; HF = heart failure; LVEF = left ventricular ejection fraction; ACE-I= angiotensin converting enzyme inhibitors; US = United States; CMIS = Charlson co-morbidity Index Score

Table 2 presents a summary of single predictor studies exploring laboratory results variables. Three different variables were investigated (NT-pro B-type natriuretic peptide reduction, albumin and glucose). The NT-pro B-type natriuretic peptide reduction was interesting because it investigated change over time. Unfortunately, the paper was difficult to read with possible typographical errors so it was impossible to interpret the results. Low albumin was a prognostic variable associated with a poor one year survival and thus being in the last year of life. Glucose was not a statistically significant prognostic variable, but it was measured as a continuous variable and it is suggested that both low and high glucose are associated with a poor prognosis so this effect may have been masked.

Table 2: Summary of single predictors exploring laboratory results. If values are different to column heading they are detailed individually							
Study Number	Methods Study Type (if RCT intervention follows in brackets) Mean follow up (+/-SD) in years	Participants Total N= Setting Mean age (+/-SD) years Per cent male	Outcome measure	Primary prognostic variable	Other prognostic variables (covariates) for which the primary predictor variable is adjusted	Results expressed as HR (95% CI) and corresponding P-value and adjusted for variables in the previous column	Comment
7 Bayes-Genis et al., 2005[166]	Prospective cohort Total study duration 12 months Mean follow up not stated	74 (69 analysed as 5 missing) Emergency admission in Spain with dyspnoea due to HF (specified criteria) 73.7 +/-7.5 in deceased and 71.4 +/-10.4 in survivors 61	Cardiovascular death (not specified how determined cardiovascular cause)	NT-pro B-type natriuretic peptide reduction percentage of <30% during hospitalization	Age Sex History of Hypertension, diabetes Dyslipidaemia, previous myocardial infarction previous HF, COPD)	4.4 (1.12-17.4) P =0 .03 Odds ratio (logistic regression) rather than HR	Typographic error confuse greater than for less than 30% Note wide CI, likely due to low numbers Cut off point not decided a priori Only for cardiovascular deaths, all cause deaths no difference
22 Horwich, Kalantar-Zadeh, MacLellan, & Fonarow, 2008[167]	Retrospective cohort Followed up for 5 years Mean follow up not stated	2796 (1726 analysed due to missing data) Patients referred to a single US university centre for HF management and or transplant 52 (+/-13) 51	All cause-mortality	Albumin classified as hypoalbuminaemia ≤3.4g/dL or normal >3.4g/dL	BMI category Demographics EF NYHA class Diabetes Aetiology of HF Medications (ACE I and βeta-blocker) Haemodynamics (right atrial pressure and pulmonary capillary wedge pressure Serum sodium Total cholesterol Haemoglobin Creatinine	1 year hypoalbuminaemia 2.4 (1.6-3.70 P<0.001 5 year Hypoalbuminaemia 2.1 (1.3-3.6) P<0.02	Cut off for continuous variable, albumin Low albumin was a prognostic variable associated with the last year of life

Table 2: Summary of single predictors exploring laboratory results. If values are different to column heading they are detailed individually							
Study Number	Methods Study Type (if RCT intervention follows in brackets) Mean follow up (+/-SD) in years	Participants Total N= Setting Mean age (+/-SD) years Per cent male	Outcome measure	Primary prognostic variable	Other prognostic variables (covariates) for which the primary predictor variable is adjusted	Results expressed as HR (95% CI) and corresponding P-value and adjusted for variables in the previous column	Comment
25 Issa et al., 2010[168]	RCT (Disease management programme V control) 3.6 (+/-2.2)	456 Ambulatory care in a tertiary referral centre in US Specific criteria for trial eligibility including irreversible HF of at least 6-month duration 50.2 +/- 11.4 70.4	All cause-mortality or transplant	Glycaemia defined as ≤ 100 mg/dL (5.5 mmol/L)	Gender Etiology LVEF Left ventricle diastolic diameter Creatinine level βeta-blocker therapy Functional status	1.45 (1.09-1.69) P =0 .039	Did not include intervention as prognostic variable If glucose added as a continuous variable it did not show an effect size, but "U shaped curve" ie both low and high glucose likely to increase mortality

Table 2. Summary of single predictors exploring laboratory results.

Key: RCT = randomised controlled trial; SD =standard deviation; CI = confidence intervals; HR = hazard ratio; BMI = body mass index; NYHA = New York Heart Association; HF = heart failure; ACE I= Angiotensin converting enzyme inhibitor; COPD = chronic pulmonary obstructive disease; LVEF = left ventricular ejection fraction

Table 3 is a summary of single predictor studies exploring electrocardiography or echocardiogram variables. There were five trials and three transplant waiting list studies so all were in selected populations, although broad enough to be included. Additionally the use of cardiac devices such as ICD and or biventricular pacemaker would affect the prognostic significance of these variables.

Table 3: Summary of single predictor studies exploring electrocardiography or echocardiogram variables. If values are different to column heading they are detailed individually							
Study Number	Methods Study Type (if RCT intervention follows in brackets) Mean follow up (+/- SD) in years	Participants Total N= Setting Mean age (+/-SD) years Per cent male	Outcome measure	Primary prognostic variable	Other prognostic variables (covariates) for which the primary predictor variable is adjusted	Results expressed as HR (95% CI) and corresponding P-value and adjusted for variables in the previous column	Comment
11 Brouwer et al., 1996[169]	Long term follow up of RCT (digoxin and ibopamine or placebo for 6 months then standard treatment, trial stopped as higher mortality in ibopamine group) surviving patients 2.6 (range: 2-3.9) patients who died 1.5 (range 8 days to 3.4 years)	95 (substudy of main trial who had necessary variables measured) Trial eligible patients with stable NYHA II or III disease. Took place in Holland 60 (+/-8) 86	Cardiac death, non-sudden cardiac death and non-cardiac death all by standard criteria and decided by independent physicians	Abnormal poincaire plot (abnormal defined by recognised pre-defined criteria)	LVEF Plasma norepinephrine Ventricular premature beats Presence of ventricular tachycardia	For cardiac death 4.5 (1.2-17.1) P<0.05 For sudden death 5.3 (1.0-27.5) P<0.05 Abnormal poincaire plot, increased risk of sudden death, but wide CI	Note this study explored cause of death = and postulated that sudden death had different predictors than due to progressive pump failure
13 Crijns et al., 2000[170]	Long term follow up of RCT (digoxin and ibopamine or placebo for 6 months then standard treatment, trial stopped as higher mortality in ibopamine group) 3.4 (range 2-5.4)	409 As study 12 Sinus rhythm patients: Age 67 (+/-8) 75% male Atrial fibrillation patients Age 70 (+/-7) 82% male	All cause-mortality	Presence of atrial fibrillation at baseline	Age NYHA class Serum urea Cardio thoracic ratio Diastolic BP	0.86 (0.59-1.24) P=0.42 Ie not independently associated with mortality	NB Same RCT as study 12 The generally observed higher mortality in patient with HF and atrial fibrillation seems to be related to other prognostic factors associated with atrial fibrillation

Table 3: Summary of single predictor studies exploring electrocardiography or echocardiogram variables. If values are different to column heading they are detailed individually							
Study Number	Methods Study Type (if RCT intervention follows in brackets) Mean follow up (+/- SD) in years	Participants Total N= Setting Mean age (+/-SD) years Per cent male	Outcome measure	Primary prognostic variable	Other prognostic variables (covariates) for which the primary predictor variable is adjusted	Results expressed as HR (95% CI) and corresponding P-value and adjusted for variables in the previous column	Comment
14 Doval et al., 1996[171]	Prospective cohort from RCT (GESICA) but designed a prior to be a secondary objective of the study (Amiodarone versus placebo but stratified randomisation procedure according to presence of Non sustained ventricular tachycardia therefore equal number with or without non-sustained ventricular tachycardia were on amiodarone) Mean 13 months (range 2-24 months)	516 Multicentre trial in Argentina. Advanced stable heart failure with specific eligibility criteria. angiotensin converting enzyme inhibitors unless CI 59.2 SD not stated 80.8	All cause-mortality	Presence of Non-sustained ventricular tachycardia on 24 hour Holter	Furosemide dose Systolic blood pressure Serum creatinine level Heart rate Chagas' disease as the etiology for heart failure	1.62 (1.22, 2.16) P<0.001	Note prior to ICD use Non sustained ventricular tachycardia on 24 hour Holter

Table 3: Summary of single predictor studies exploring electrocardiography or echocardiogram variables. If values are different to column heading they are detailed individually							
Study Number	Methods Study Type (if RCT intervention follows in brackets) Mean follow up (+/- SD) in years	Participants Total N= Setting Mean age (+/-SD) years Per cent male	Outcome measure	Primary prognostic variable	Other prognostic variables (covariates) for which the primary predictor variable is adjusted	Results expressed as HR (95% CI) and corresponding P-value and adjusted for variables in the previous column	Comment
15 Fosbøl et al., 2008[172]	Prospective cohort of the DIAMOND (Dofetilide V placebo) Total study duration RCT 3 years then follow up for at least 10 years for this study Mean follow up not stated	1518 Hospitalised patients, 37 centres in Denmark and meet trial eligibility criteria Median age 71 years (5%, 95% percentiles; 51-84) 73	All-cause mortality	10ms increase in mean QRS over 3 year period,	Age Sex Wall Motion Index NYHA Renal function (calculated creatinine clearance) Resting heart rate PR interval QRS duration at baseline History of myocardial infarction, chronic obstructive pulmonary disease, smoking status, and diabetes	1.02, (1.00-1.04) P = 0.03 ,	Adding intervention (dofetilide) into model made no difference Widened QRS, increased mortality Small effect, CI close to 1. Low use of Beta blockers and aldosterone inhibitors and importantly prior to widespread use of cardiac devices especially biventricular pacemakers
21 Hofmann, Bauer, Handrock, Weidinger, & Goedel-Meinen, 2005[173]	RCT Val-HeFT (Valsartan V placebo) International trial but subgroup of German centres 25.8 +/- 5 months	248 NYHA class II-IV, > 3 months, E F <40% and trial eligibility criteria on ACE-Is, Beta-blockers, diuretics, or digoxin unless CI 60 (range 29-82 years)	All-cause mortality	Longest mean QRS (average of 3 cycles) in any of 12 leads measured in ms	Gender Age Atrial fibrillation NYHA classification LVEF	1.0 (1.0–1.1) P<0.008	Note CI just at 1 so only just statistically increased risk of death. Angiotensin converting enzyme inhibitors, Beta blockers, used and patients with pacemaker excluded. Intervention not included in model

Table 3: Summary of single predictor studies exploring electrocardiography or echocardiogram variables. If values are different to column heading they are detailed individually							
Study Number	Methods Study Type (if RCT intervention follows in brackets) Mean follow up (+/- SD) in years	Participants Total N= Setting Mean age (+/-SD) years Per cent male	Outcome measure	Primary prognostic variable	Other prognostic variables (covariates) for which the primary predictor variable is adjusted	Results expressed as HR (95% CI) and corresponding P-value and adjusted for variables in the previous column	Comment
		83					
17 Gavazzi et al., 1997[174]	Prospective cohort study 11.1 months range (1 to 48 months)	142 Consecutive ambulatory patients with chronic advanced HF referred for treatment and evaluation for transplant to centre in Italy EF≤35% Symptoms despite optimal standardised therapy for at least a month 49.7 (range 15 to 65) 92	All- cause mortality Patients who died before transplant were treated as uncensored, whereas remaining patients were treated as censored with censoring being either transplant or the end of the study	RVEF measured by thermodilution (details in paper)	Dilated cardiomyopathy Heart Failure Score	0.9148 (0.878-0.954) P=0.000	Transplant waiting list patients, selected population, no comorbidities young age and most likely due to idiopathic dilated cardiomyopathy. Note dilated cardiomyopathy was protective, ie less likely to die
23 Huang, Young, & Wei, 2000[175]	Retrospective cohort 12 +/-9 months	119 12 +/-9 Consecutive ambulatory patients with end stage HF referred for heart transplant to clinic	All- cause mortality	Total pulmonary vascular resistance ≥14 Wood units Cardiac Index	All other potential prognostic indicators were not significant on univariate and multivariate analysis and so not included in the model	Total pulmonary vascular resistance -0.45 (-0.77,-0.13) P=0.0063 Cardiac Index -0.96 (-1.71,-0.41) P=0.0213	As above re transplant

Table 3: Summary of single predictor studies exploring electrocardiography or echocardiogram variables. If values are different to column heading they are detailed individually							
Study Number	Methods Study Type (if RCT intervention follows in brackets) Mean follow up (+/- SD) in years	Participants Total N= Setting Mean age (+/-SD) years Per cent male	Outcome measure	Primary prognostic variable	Other prognostic variables (covariates) for which the primary predictor variable is adjusted	Results expressed as HR (95% CI) and corresponding P-value and adjusted for variables in the previous column	Comment
		in China. Strict eligibility criteria 49 +/- 14 76					
29 Pinsky, Sciacca, & Steinberg, 1997[176]	Prospective cohort 201 days no SD	108 referral, 80 placed on list Consecutive referrals to heart transplant clinic in US Strict criteria for transplant 51 +/-8 79	All- cause mortality	QT dispersion in ms	Age Gender Ischaemic aetiology Previous ventricular tachycardia Atrial fibrillation	6.77 (1.19, 38.5) P value not stated QT dispersion increased risk of death	As above re transplant Age was included in model although non-significant, this could be because very selected group, older patients not eligible for transplant

Table 3. Summary of single predictor studies exploring electrocardiography or echocardiogram variables.

Key: RCT = randomised controlled trial; SD =standard deviation; CI = confidence intervals; HR = hazard ratio; BMI = body mass index; NYHA = New York Heart Association; HF = heart failure; BP = blood pressure; EF = ejection fraction; ICD = implantable cardiac defibrillator; ACE-I= angiotensin converting enzyme inhibitors; RVEF = Right Ventricular Ejection Fraction; US = United States

Table 4 is a summary of single predictor studies exploring clinical variables. There was a variety of designs. Three studies explored BMI including one measuring change in BMI.

	Study Number					
	4 Andreas, Hagenah, Moller, Werner, &Kreuzer, 1996[177]	8 Bittner et al., 1993[178]	16 Gastelurrutia et al., 2011[179]	27 Kenchaiah et al., 2007[180]	30 Pocock et al., 2008[181]	31 Shahar et al., 2004[182]
Methods Study Type (if RCT intervention follows in brackets) Mean follow up (+/- SD) in years	Prospective cohort 32 months (+/- 15months)	Prospective cohort Studies of Left Ventricular Dysfunction (SOLVD) Registry Substudy US, Canada, Belgium 242 (+/-82 days)	Longitudinal study Median of 44 months interquartile range 34-46 months	As study 1	As study 1	Longitudinal cohort study 5.5 SD not stated
Participants Total N= Setting Mean age (+/-SD) years Per cent male	36 LVEF<40%, admitted to cardiology, in Germany, strict criteria including <75 years 54+/-12 86.2	898 but 65 did not walk therefore results analysed for 833 A large, well-characterized subset of patients with left ventricular dysfunction from differing causes and of differing severity who underwent the 6-minute walk test Diagnostic criteria for heart failure LVEF of ≤0.45 or radiological evidence of heart failure and specific eligibility criteria	Multicentre study in Spain, ambulatory heart failure patients recruited from University hospital specialist clinics Symptomatic heart failure (NYHA class II or III), and could have reduced or preserved LVEF	As study 1	As study 1	2887 All hospitals in Minneapolis, and all patients hospitalised with heart failure (wide criteria) but only included patients aged 35 to 84 mean age not stated 51

	Study Number					
	4 Andreas, Hagenah, Moller, Werner, &Kreuzer, 1996[177]	8 Bittner et al., 1993[178]	16 Gastelurrutia et al., 2011[179]	27 Kenchaiah et al., 2007[180]	30 Pocock et al., 2008[181]	31 Shahar et al., 2004[182]
		59 +/-12 78				
Outcome measure	Death but also included 2 patients that were transplanted	All-cause mortality	All-cause mortality	As study 1	As study 1	All-cause mortality
Primary prognostic variable	Cheyne-Stoke respiration (CSR) which was considered present when there were at least 3 regular cycles of increasing and decreasing air flow as well as increasing and decreasing thoracic and abdominal efforts.	Distance walked in 6 minutes measured in meters	BMI included as both a continuous variable and also as a categorical variable, Lean (≤24.9 kg/m2), Overweight (25.0-29.9 kg/m2), Obese (≥30.0 kg/m2) Used Lean as the reference variable ie HR for lean =1	BMI as continuous variable per 1-kg/m^2 decrease BMI as categorical variable <22.5 kg/m^2 22.5 to 24.9 kg/m^2 25 to 29.9 kg/m^2 30 to 34.9 kg/m^2 ≥35 kg/m^2	Percentage weight change over 6 months (> -5%, -5 to -1%, -1 to +3% >+3%) at different BMI categories <22.5 kg/m^2 22.5–30 kg/m^2 >30 kg/m^2	Gender Male Age LVEF
Other prognostic variables (covariates) for which the primary predictor variable is adjusted	Nil	LVEF Cause (stayed in even though non-significant as registry stratified by cause)	Prior history of myocardial infarction Hypertension LVEF NT-proBNP	Age LVEF Diabetes mellitus Gender NYHA Smoking status Bundle-branch block Cardiomegaly, Previous hospitalization for HF Diastolic blood pressure Duration of HF. Previous myocardial infarction Oedema Heart rate	As 28 but not Heart rate Pulmonary crackles Pulmonary oedema Mitral regurgitation Atrial fibrillation, Rest dyspnoea	No other variables but adjusted for two other variables out of age, sex and LVEF Age 35-64 was used as a reference value

	Study Number					
	4 Andreas, Hagenah, Moller, Werner, &Kreuzer, 1996[177]	8 Bittner et al., 1993[178]	16 Gastelurrutia et al., 2011[179]	27 Kenchaiah et al., 2007[180]	30 Pocock et al., 2008[181]	31 Shahar et al., 2004[182]
				Pulmonary crackles Pulmonary oedema Mitral regurgitation Atrial fibrillation, Rest dyspnoea Study treatment (candesartan versus placebo)		
Results expressed as HR (95% CI) and corresponding P-value and adjusted for variables in the previous column	When survival between the groups stratified by the amount of CSR was analysed after 3 months, there were more deaths in the group with >20% CSR corrected for total sleep time than in the group with <20%, although this difference was not significant (4 of 20 vs 1 of 16; chi-square test, p = 0.24)	OR, 1.50 for each 120-m decrement in distance walked; (1.11 to 2.03) P<0.05 The lower the distance walked, the increased risk of death	An increase of 1 unit in BMI; HR = 0.94, (0.91-0.97) P =0.0003 Lean (reference) HR=1 Overweight 0.77 (0.57, 1.04) P=0.089 (ie not significant) Obesity 0.59 (0.42, 0.83) P=0.003	BMI as continuous variable per 1-kg/m^2 decrease 1.03 (1.02 to 1.04) P=0.0001 BMI as categorical variable <22.5 kg/m^2 1.69 (1.43 to 2.01) P=0.0001 22.5 to 24.9 kg/m^2 1.46 (1.24 to 1.71) P=0.0001 25 to 29.9 kg/m^2 1.22 (1.06 to 1.41) P=0.005 30 to 34.9 kg/m^2 1.00 (referent) ≥35 kg/m^2 1.17 (0.95 to 1.43) P= 0.13	**<22.5 kg/m2** > -5% 2.56 (1.76, 3.73) -5 to -1% 1.50 (1.13, 1.99) -1 to +3% 1.53 (1.20, 1.95) > +3% 1.60 (1.24, 2.07) **22.5–30 kg/m2** > -5% 1.54 (1.22, 1.95) -5 to -1% 1.31 (1.10, 1.55) -1 to +3% 1 (reference) **>30 kg/m2** > -5% 1.66 (1.21 2.27) -5 to -1% 0.95 (0.75,1.21) -1 to +3%	Gender 1.29 (1.18-1.41) Age 65-74 1.61 (1.40-1.84) 75-84 2.27 (2-2.58) LVEF (%) >45 Reference value 26-45 1.12 (0.94–1.35) ≤25 1.52 (1.27–1.83) Missing 1.54 (1.32–1.79**)**

	Study Number					
	4 Andreas, Hagenah, Moller, Werner, &Kreuzer, 1996[177]	8 Bittner et al., 1993[178]	16 Gastelurrutia et al., 2011[179]	27 Kenchaiah et al., 2007[180]	30 Pocock et al., 2008[181]	31 Shahar et al., 2004[182]
					0.90 (0.73, 1.11) > +3% 1.07 (0.84, 1.37	
Comment	Note Chi squared test not cox regression and not adjusted for other variables, Also small numbers and highly selected population	Note 65 excluded because did not walk Very few patients NYHA IV Note same registry as study 9	Obesity paradox ie BMI inversely associated with mortality but did not look at low body weight as this is may be associated with increased mortality	CHARM as 1, 34 etc.. This showed weight loss is associated with increased mortality different referent variable to study 16 and not significant in the ≥35 kg/m^2 group	CHARM as 1, 34 etc.. Difficult to know which results to record Weight gain had a modestly increased mortality risk but even stronger links between weight loss and dying P values not given, but can work out if sig from CI, if sig don't cross reference value of 1 Interesting because time updated analysis	P values not given but based on CI LVEF of 26-45 is not a significant predictor of mortality, this could be because of the reference value given would include patients with diastolic HF

Table 4. Summary of single predictors exploring clinical variables.

Key: RCT = randomised controlled trial; SD =standard deviation; CI = confidence intervals; HR = hazard ratio; BMI = body mass index; NYHA = New York Heart Association; HF = heart failure; BP = blood pressure; EF = ejection fraction; ICD = implantable cardiac defibrillator; ACE-I= angiotensin converting enzyme inhibitors; RVEF = Right Ventricular Ejection Fraction; US = United States; NT-proBNP = N terminal Pro Brain Natriuretic Hormone

Table 5 presents a summary of studies which explore multiple variables. All of the studies (apart from 5 and 29) examined a large list of variables and those that were positive on log rank test were evaluated in multivariate Cox proportional hazard analysis and those that were independent prognostic predictors were subsequently included in the final model. Study 6 included all variables even those that were not independent predictors of mortality.

Table 5: Summary of studies exploring multiple variables. If values are different to column heading they are detailed individually					
Study Number	Methods Study Type (if RCT intervention follows in brackets) Mean follow up (+/- SD) in years	Participants Total N= Setting Mean age (+/-SD) years Per cent male	Outcome measure	Results expressed as HR (95% CI) and corresponding P-value and adjusted for all other variables in the model	Comment
6 Barnes et al., 2008[183]	Prospective cohort study Not stated	542 UK Primary Practice Pragmatic approach, search for Read code for heart failure or angiotensin converting enzyme inhibitors or loop diuretic and then checked by GP Patients > 60 years, did not have evidence of significant cognitive impairment, and had self- reported symptomatic heart failure NYHA classification II-IV median age 77 Interquartile range 71-82 54	All-cause mortality	Female gender 0.42 (0.25–0.72) P=0.002 Baseline NYHAIII or IV 1.83 (1.09–3.08) P=0.023 Living with others 1.05 (0.64–1.74) P= 0.853 Symptoms of depression 0.89 (0.51–1.54) P=0.671 Socio-economic group III–V 1.05 (0.64–1.72) P= 0.860 Co-morbidities: Arthritis 0.76 (0.46–1.27) P= 0.297 Lung disease 0.96 (0.57–1.61) P=0.885 Diabetes 1.31 (0.75–2.29) P= 0.346 Stroke 0.84 (0.45–1.57) P= 0.580 Cancer 1.77 (0.98–3.20) P= 0.060 Neurological 2.21 (0.66–7.39) P=0.197 Other 0.88 (0.51–1.52) P= 0.641 Age-group (relative to<65 years) P=0.001 65–69 1.02 (0.22–4.60)	Note older population, had to be >60 to be in study Included all examined variables in Cox proportional hazard regression, even those that were not significant i.e. living alone or with others, co-morbidities apart from cancer, symptoms of depression, or socio-economic group. Not all of the age groups were significant either, even though P value only given for relative to <65 years Variables readily available to GPs where most heart failure patients are diagnosed and treated

Table 5: Summary of studies exploring multiple variables. If values are different to column heading they are detailed individually					
Study Number	Methods Study Type (if RCT intervention follows in brackets) Mean follow up (+/- SD) in years	Participants Total N= Setting Mean age (+/-SD) years Per cent male	Outcome measure	Results expressed as HR (95% CI) and corresponding P-value and adjusted for all other variables in the model	Comment
				70–74 1.80 (0.51–6.40) 75–79 1.89 (0.51–7.07) 80–84 4.18 (1.22–14.30) 85> 5.03 (1.43–17.62)	
9 Bourassa et al., 1993[184]	Prospective cohort study All followed up at one year	6273 but calculated on 6065 as 208 missing participants SOLVD multinational register (US, Canada Belgium) LVEF<45% or radiological evidence of pulmonary congestion 62 +/- 12 74	All-cause mortality	In the multivariate analysis, age, LVEF female gender, diabetes meliitus and atrial fibrillation were independently related to mortality, in patients with ischemic heart disease (roughly 70% of the SOLVD Registry population)	No values given Only for patients with ischaemic heart disease, not explained why only looked at that group of patients but SOLVD register as 8 and stratified on cause to enter registry
10 Brophy, Deslauriers, & Rouleau, 1994[185]	Prospective cohort study 44 months, range 41 to 47 months	153 One teaching hospital and one community hospital All patients presenting to ED with decompensated HF 70.6 +/-9.7 58	All-cause mortality	A prior admission for HF 1.9 (1.2-2.9) P=0.005 Presence of an intraventricular conduction delay 1.9 (1.2-2.9) P=0.003 The cumulative dose of intravenous furosemide 1.7 (1.2-3.5) P<0.005 Were all associated with increased risk of death	Long list of variables (available on admission to emergency room) significant variables on log rank test were evaluated in multivariate Cox proportional hazard analysis
18 Gronda et al., 1999[186]	Retrospective cohort 2 SD not stated	125 Consecutive transplant waiting list patients hospitalised for the need to initiate IV pharmacological circulatory support from one centre in Italy 49	All-cause mortality but patients who were transplanted or LVAD were excluded from analysis (37 patients)	Duration of pharmacologic circulatory support 1.08 (1.03-1.14) Blood urea nitrogen at admission 1.02 (1.00-1.04) Peak serum bilirubin level 1.63 (1.16-2.28) Ventricular arrhythmias 2.80 (0.93-	Highly selected population, transplant waiting list and on IV pharmacological circulatory support Small numbers Long list of variables considered and those that were independent predictors on Cox proportional

Table 5: Summary of studies exploring multiple variables. If values are different to column heading they are detailed individually					
Study Number	Methods Study Type (if RCT intervention follows in brackets) Mean follow up (+/- SD) in years	Participants Total N= Setting Mean age (+/-SD) years Per cent male	Outcome measure	Results expressed as HR (95% CI) and corresponding P-value and adjusted for all other variables in the model	Comment
		range 16-64 89		8.41) P values not given	hazard analysis
19 Gustafsson et al., 2003[187]	RCT DIAMND-CHF study (dofetilide v placebo) Mean follow up not stated follow up 5 to 8 years	5548 (57 missing data, therefore 5491 analysed) Hospitalised patients from 34 centres in Denmark NYHA functional class III or IV Strict eligibility criteria 71.7+/- 10.2 60	All-cause mortality	Wall motion index (per unit increase) 0.60 (0.56–0.64) Age (per year) 1.04 (1.03–1.04) Male gender 1.26 (1.17–1.36) Diabetes 1.42 (1.30–1.56) Valve disease 1.40 (1.18–1.65) Creatinine clearance (denotes the risk reduction associated with an increase in creatinine clearance of 20 ml/min) 0.73 (0.69–0.77) Duration of heart failure (per month) 1.002 (1.001–1.003) COPD 1.36 (1.25–1.47) P values not given	Note including participants with diastolic failure List of variables included those that were significant predictors of mortality as described above
24 Huynh, Rovner, & Rich, 2006[188]	Long term follow up from RCT (Nurse-directed multidisciplinary intervention designed to reduce the risk of re-hospitalization v usual care) Not stated, but follow up for up to 14 years	282 Follow up from RCT, elderly patients (>70) at risk of hospitalisation, one medical centre in US 78.4 ± 6.1 (control group, n= 140) 80.1 ± 5.9 (treatment group, n= 142) 26	All-cause mortality	Age, per 5 y 1.14 (1.03-1.26) P=0.01 Serum sodium<135 mEq/L 1.67 (1.19-2.32) P=0.003 Coronary Artery Disease 1.51 (1.16-1.95) P=0.002 Dementia 2.02 (1.13-3.61) P=0.02 Peripheral Vascular Disease 1.74 (1.20-2.52)	List of variables and selected as per previous Note elderly participants but still trial population, diagnosis of heart failure not clear and LVEF excluded as missing data and as long follow up prior to beta blockers and aldosterone antagonists being widely used Intervention not included in model

Table 5: Summary of studies exploring multiple variables. If values are different to column heading they are detailed individually					
Study Number	Methods Study Type (if RCT intervention follows in brackets) Mean follow up (+/- SD) in years	Participants Total N= Setting Mean age (+/-SD) years Per cent male	Outcome measure	Results expressed as HR (95% CI) and corresponding P-value and adjusted for all other variables in the model	Comment
				P=0.004 Systolic BP, per 10 mm Hg 0.95 (0.92-0.98 P=0.004 Serum urea nitrogen per 10 mg/dL 1.20 (1.12-1.29 P<0.001	
26 Kearney et al., 2002[189]	Prospective cohort study 4.3 SD not stated	553 Cardiology outpatient clinics of eight UK general hospitals, consecutive patients of either gender, age 18 to 85 years, with chronic heart failure were recruited on the basis of predefined inclusion and exclusion criteria 62.7 +/- 9.7 76	All-cause mortality	Standard deviation of all normal-to normal RR intervals decrement (10%) 1.05 (1.01–1.08) p=0.006 Serum creatinine increment (10 µmol/l) 1.09 (1.06–1.12) p< 0.001 Serum sodium (2 mmol//l) 1.14 (1.06–1.24) p< 0.001 Cardiothoracic ratio (10%) increment 1.23 (1.10–1.37) p<0.001 Non sustained ventricular tachycardia (present) 1.57 (1.20–2.05) p=0.001 LVESD (1 cm) increment 1.23 (1.08–1.39) p=0.002 LVH (present) 1.54 (1.06–2.23) p=0.023 Age (10 yr) increment 1.19 (1.02–1.38) p=0.027	List of variables and selected as previous Prior to widespread use of beta blockers and aldosterone antagonists Restricted population for example excludes patients with diabetes and generally younger age

Table 5: Summary of studies exploring multiple variables. If values are different to column heading they are detailed individually					
Study Number	Methods Study Type (if RCT intervention follows in brackets) Mean follow up (+/- SD) in years	Participants Total N= Setting Mean age (+/-SD) years Per cent male	Outcome measure	Results expressed as HR (95% CI) and corresponding P-value and adjusted for all other variables in the model	Comment
28 Ko et al., 2008[55]	Prospective cohort (chart review) Median follow up 6 years SD or range not stated	9 943 Acute care hospitals in Ontario, Canada Newly hospitalised, with primary diagnosis of HF 75.8 +/- 11.5 49.6	Median survival months (95% CI)	All patients 29 (28-30) EFFECT HF risk score* Very low Not able to work out as insufficient number of death Low 59 (55-62) Intermediate 25 (24-27) High 8 (7-9) Very high 3 (2-4) P values not given	Prior to widespread use of beta-blockers, ACE-Is etc.. Looked at median survival rather than HRs

Table 5. Summary of studies involving multiple variables.

Key: RCT = randomised controlled trial; SD =standard deviation; CI = confidence intervals; HR = hazard ratio; BMI = body mass index; NYHA = New York Heart Association; HF = heart failure; BP = blood pressure; LVEF = left ventricular ejection fraction; ICD = implantable cardiac defibrillator; LVAD = left ventricular assist device; ACE-I= angiotensin converting enzyme inhibitors; RVEF = Right Ventricular Ejection Fraction; UK = United Kingdom; GPs = general practitioners; US = United States; NT-proBNP = N terminal Pro Brain Natriuretic Hormone; ED = emergency department; COPD = chronic pulmonary obstructive disease

NB. * EFFECT-HF risk score includes variables: Age (y) Age, Respiratory rate (breaths/min), Systolic blood pressure (mm Hg), Blood urea nitrogen (mg/dL), Hyponatremia (<136 mEq/L), Cerebrovascular disease, Dementia, Chronic obstructive pulmonary disease, Hepatic cirrhosis, Cancer, Haemoglobin <g/dL

~Heart failure clinical prediction rule includes variables: demographic (Gender), Historical (Coronary artery disease, angina, percutaneous transluminal coronary angiography, diabetes, and lung disease), Vital signs (Systolic blood pressure, pulse, respiratory rate, and temperature) Laboratory (Blood urea nitrogen, sodium, potassium, creatinine, glucose, white blood cell count, and arterial pH), Electrocardiographic (Acute myocardial infarction and acute

Table 6 contains two studies exploring the Seattle Heart Failure Model. The Seattle Heart Failure Model (SHFM) requires following variables: age, sex, NYHA functional class, systolic blood pressure, and weight), medications (angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, beta-blocker, statin, aldosterone blocker, loop diuretic dose, and allopurinol), device therapies (implantable cardioverter-defibrillator, cardiac resynchronization therapy), and results of diagnostic testing (ejection fraction, lymphocyte percentage, and levels of sodium, haemoglobin, uric acid, and total cholesterol). In the study by Haga et al., 2012[112] the SHFM score also included ischaemic aetiology for heart failure and QRS >120 ms and compared the SHFM prognostic utility with that of the Gold Standards framework (GSF) criteria for heart failure: 1. NYHA stage III or IV heart failure; 2. The 'surprise question' (to be asked of a healthcare provider familiar with the patient, included for all patients in this study) "Would you be surprised if this patient died in the next 6-12 months?"; 3. Repeated hospital admissions with symptoms of heart failure; 4. Difficult physical or psychological symptoms despite optimised tolerated therapy.

Table 6: Summary of studies exploring the Seattle Heart Failure Model. If values are different to column heading they are detailed individually							
Study Number	Methods Study Type (if RCT intervention follows in brackets) Mean follow up (+/- SD) in years	Participants Total N= Setting Mean age (+/-SD) years Per cent male	Outcome measure	Prognostic variables in model	Other prognostic variables (covariates) for which the primary predictor variable is adjusted	Results expressed as HR (95% CI) and corresponding P-value and adjusted for variables in the previous column	Comment
3 Allen et al., 2008[190]	Cohort study 3.1 Interquartile range 2.7-3.3 years	122 Academic centre in US ambulatory consecutive patients to heart failure disease management programme 61 IQR 53-74years 62	All-cause mortality	LER of patient predicted to SHFM* predicted life expectancy for each individual participant Under estimated LER<0.7 Concordant 0.7-1.3 (reference value) Over-estimated >1.3	Age Sex Race NYHA class LVEF aetiology of HF	No difference between LER and survival overestimated LER, 1.05 (0.46-2.42) P = 0.91 underestimated LER, 0.45 (0.17-1.21) P =0 .11	SHFM derived from trial data but been validated in ambulatory populations
20 Haga et al., 2012[112]	Prospective cohort All followed up at one year	138 All community based ambulatory patients from a clinical database used by heart failure nurse specialists, in a single Health authority in Scotland. All had NYHA class III or IV symptoms, excluded if due to be discharged from HFNS in next 6 weeks	All cause-mortality	GSF# At least 2 out of 4 *The SHFM to calculated expected mean life expectancy of <1 year Serum creatinine as a single factor less	Nil	GSF sensitivity of 83%, specificity of 22%, positive predictive value (PPV) of 33%, negative predictive value (NPV) of 5%, overall accuracy of 41% SHFM sensitivity of 12%, specificity of 99%, PPV of 83%, NPV of 71%,	Sensitivity and specificity analysis was performed in comparison with death at 1 year Very relevant population for GPRD study Study highlights the difficulty in predicting the last year of life in patients with HF even where they are well known to the caregiver

Table 6: Summary of studies exploring the Seattle Heart Failure Model. If values are different to column heading they are detailed individually							
Study Number	Methods Study Type (if RCT intervention follows in brackets) Mean follow up (+/- SD) in years	Participants Total N= Setting Mean age (+/-SD) years Per cent male	Outcome measure	Prognostic variables in model	Other prognostic variables (covariates) for which the primary predictor variable is adjusted	Results expressed as HR (95% CI) and corresponding P-value and adjusted for variables in the previous column	Comment
				than or greater 140µmol/L		overall accuracy of 72%. Serum creatinine sensitivity of 56% ; specificity of 72%; PPV of 56%; NPV of 79%, overall accuracy of 72%	and where extensive clinical data are used to predict prognosis GSF not specific especially in frail elderly as HFNS felt sudden death very likely, SHFM, underestimates perhaps because validated in trial population Serum creatinine as a single variable with the highest sensitivity and specificity for predicting death at 12 months, not usually identified as factor as models often derived from populations with normal creatinine

Table 6. Summary of studies exploring the Seattle Heart Failure Model.

Key: RCT = randomised controlled trial; SD =standard deviation; CI = confidence intervals; IQR= inter-quartile range; HR = hazard ratio; NYHA = New York Heart Association; SHFM = Seattle Heart Failure Model; LER =Life expectancy ratio; HF = heart failure; GSF = Gold Standards Framework; LVEF = left ventricular ejection fraction; HFNS = heart failure nurse specialists; US = United States; GPRD = general practice research database

A risk of bias assessment was undertaken using a framework described by Hayden and co-authors.[144] This is outlined in **appendix four.** It is described as a list of six questions with answers, yes, partly, no and unsure. For the purpose of the risk of bias assessment, the categories were changed to low, intermediate and high risk of bias if the answers to the framework questions were yes (low risk), partly (intermediate risk) or no/unsure (high risk). The results of the assessment are outlined in **table 7**.

Table 7: Risk of bias assessment for each included study

	Analysis	Confounding measurement and account	Outcome measurement	Prognostic factor measurement	Study attrition	Study participation
1 Abrahamsson et al., 2009	L	I	L	L	I	L
2 Adams Jr et al., 1999	L	I	L	L	I	L
3 Allen et al., 2008	L	I	L	L	I	L
4 Andreas et ali., 1996	L	L	L	I	I	I
5 Auble, T.E., et al., 2005	L	L	L	L	I	I
6 Barnes et al., 2008	L	I	L	I	L	I
7 Bayes-Genis et al., 2005	I	L	L	I	I	L
8 Bittner et al., 1993	L	I	L	L	I	L
9 Bourassa et al., 1993	L	I	L	I	L	I
10 Brophy, Deslauriers, &Rouleau, 1994	I	L	L	L	I	L
11 Brouwer et al., 1996	I	L	L	I	I	L
12 Chin& Goldman, 1998	I	L	L	L	L	L
13 Crijns et al., 2000	L	I	L	L	L	L
14 Dovalet al., 1996	L	L	L	L	L	I
15 Fosbøl et al., 2008	L	I	L	L	I	L
16 Gastelurrutia et al., 2011	L	L	L	L	I	I
17 Gavazzi et al., 1997	L	L	L	I	I	L
18 Gronda et al., 1999	I	L	L	I	I	L
19 Gustafsson et al., 2003	L	I	L	L	I	L
20 Haga et al., 2012	L	L	L	L	I	I
21Hofmann al., 2005	L	L	L	L	I	I
22 Horwichal., 2008	L	L	L	L	I	L
23 Huang, Young, & Wei, 2000	L	L	L	L	I	I
24 Huynh, Rovner, & Rich, 2006	L	L	I	I	I	L
25 Issa et al., 2010	L	I	L	L	I	I
26 Kearney et al., 2002	I	I	L	L	I	L
27 Kenchaiah et al., 2007	L	I	L	L	I	L

Table 7: Risk of bias assessment for each included study						
28 Ko et al., 2008	L	I	L	L	I	I
29 Pinsky, Sciacca, & Steinberg, 1997	I	L	L	L	I	I
30 Pocock et al., 2008	I	L	L	L	L	L
31 Shahar et al., 2004	L	I	I	L	I	L
32 Solomon et al., 2007	I	L	L	L	I	L
Key L= Low risk of bias, modified Hayden score 2, answer to framework question is yes H= High risk of bias, modified Hayden score 0, answer to framework question is no or unsure I= Intermediate risk of bias, modified Hayden score 1, answer to framework question is partly						

Table 7. 'Risk of bias' assessment for each included study

Variables such as age and sex, medications, blood tests and other investigations such as blood pressure values and diagnoses can be found in the GPRD, but are entered as Read codes. Therefore, as variables to search for in the GPRD, these are only useful for diseases that are well defined and routinely recorded by GPs using Read codes, for example those diseases described by Quality and Outcomes Framework (QOF). **Table 8** outlines the prognostic variables outlined in this review that could potentially be also found in GPRD.

Table 8: Prognostic variables that could potentially be found in GPRD	
Category of variable	Specific prognostic variable
Demographic	Gender
Laboratory results	Albumin Glycaemia Serum creatinine
EFFECT score	All variables in score apart from respiratory rate and presence of hepatic cirrhosis
Seattle Heart Failure Model	All variables apart from NYHA functional class, LVEF or presence of device therapy (and for modified score not QRS interval or if ischaemic aetiology for HF)

Table 8. Prognostic variables that could potentially be found in GPRD

3.6 Discussion

3.6.1 Achievement of aim of the review

The aim of the review was to determine prognostic markers associated with the last year of life in adult patients with heart failure. Even with the exclusion of poor quality studies a plethora of studies of prognostic variables remained. These included demographic, laboratory, electrocardiography, echocardiogram and clinical variables as well as studies that developed models from multiple variables. Despite this huge number of possibilities, no clinically useful prognostic predictors of the last year of life were found in this systematic review.

The primary variables are often only studied once, but even for the few that were investigated more than once, such as gender or BMI, were adjusted for by different covariates and so could not be combined in a meta-analysis. Even more importantly, as they were adjusted by different covariates and /or non-significant covariates were removed from the model it was impossible to assess if they offered any additional prognostic information to the variables under primary study, or were just confounding variables.

The large number of possible prognostic variables is reflected in work by other authors. A narrative (non-systematic) review of prognostic variables in heart failure identified over 300 proposed prognostic variables for heart failure[191]. Another author has remarked that new prognostic variables for heart failure are being discovered almost continuously[192]. A review article discussing systematic reviews of prognosis has also highlighted the large number of systematic reviews that have found many prognostic variables but are not able to draw conclusions whether they are useful, or not[143].

Unsurprisingly, given this difficulty, neither was the secondary objective to identify the best predictors of being in the last year of life, achieved. This was not only because of the inability to compare the same variable between studies (meta-analysis) but also because different covariates were used to correct for confounding, so the relative strength of each variable as a predictor could not be compared. Again, this is commonly seen in other systematic reviews of prognostic markers and it has been argued that traditional meta-analysis is unhelpful in

prognostic systematic reviews and individual patient level data should be used instead[147].

Furthermore, many of the studies were in restricted populations such as trial patients (with strict eligibility criteria); cohort studies (often with small numbers) or patients awaiting transplant (who tend to be younger and do not have co-morbidities) and so do not represent the general heart failure population. This is called spectrum bias[193].

Another difficulty with studies that are not representative of the general heart failure patients is that the exclusion criteria can in themselves be important prognostic variables. For example, patients with impaired renal function are often excluded from studies, but abnormal serum creatinine, a measure of renal function is an important prognostic variable in heart failure[112]. A similar pattern is seen in multi-morbidity. Patients with co-morbid conditions are often excluded from studies, but co-morbidity is likely to be an important prognostic variable[194]. Hospitalisation is often used as an entry criterion for studies, but again, this means it cannot be assessed as a prognostic variable.

So despite the many prognostic variables found in the published literature, it was difficult to determine their clinical usefulness in a real world heart failure population.

Another objective was to find prognostic variables that may be useful in the GPRD study (**chapter four**). Possible variables were found and are detailed in **table 8**. However, in view of spectrum bias, discussed above, creatinine was selected as this was found in a population similar to that of GPRD; UK primary care[112].

3.6.2 **Methodological issues with the reviewed studies**

There were additional methodological problems, even beyond those assessed by the risk of bias tool. Prognostic variables are often reported in a single study only, and then not validated on a separate sample[195]. Many of the other prognostic models using multiple variables that were identified have not been validated in separate populations to the original study population. In contrast, the Seattle Heart Failure Model (SHFM), although designed from trial data, *has* been validated in large cohort studies, including in the community [192, 196, 197]. However, despite this

potential, the one study which tested its utility in identifying patients in the last year of life did not find a clinically useful sensitivity despite a high specificity[112].

An additional issue is that prognostic variables may change in relevance with changes in the population, most notably with changes in therapeutics. Prognostic variables that were identified in populations prior to the widespread use of beta-blockers, angiotensin converting enzyme inhibitors, aldosterone antagonists and the use of cardiac devices would now needed to be updated in contemporary populations[192, 196, 198].

3.6.3 **Methodological issues with the systematic review**

It is more difficult to search for relevant publications in prognosis systematic reviews than for systematic reviews exploring effectiveness of interventions[147]. In this review, this challenge was addressed by using a wide, comprehensive search strategy and extensive database searching to improve the yield of suitable studies.

Critical appraisal or assessment for risk of bias of included studies is a vital part of a systematic review. As systematic reviews of prognostic factors are less well developed there were no suitable tools[147], so a tool was created based a methodological systematic review by Hayden and colleagues[144] (see **appendix four**). This tool was piloted during the study and was felt by the student and her supervisors to be helpful. During the period of this review the National Institute for Health and Clinical Excellence (NICE) has subsequently produced a methodology checklist for prognostic studies based on the Hayden study providing further justification for its use[199].

Publication bias is a particular concern. Epidemiological studies are more prone to publication bias than effectiveness trials with statistically significant prognostic variables being more likely to be published[147]. This review searched "the grey literature" including conference proceedings, thesis databases and trial databases. However, it remains a limitation of the review. Especially, as many of the studies were secondary analysis of data collected for other reasons, (e.g. trial data) it is likely that statistically non-significant variables were not published anywhere and the statistically positive results may be due to chance or "data dredging" and so should be interpreted cautiously[147, 193]. It has been proposed that prognostic studies should

be prospectively designed and their protocols published and registered in a similar way to clinical trials for interventions to reduce this problem[143].

3.6.4 **Heart failure factors**

Heart failure is a clinical syndrome (**section 1.4**) rather than a distinct disease entity and there are many different definitions of heart failure. As discussed in **section 1.4** and **appendix six** there is an additional factor of heart failure with 'preserved' EF. Heart failure is treated in different settings, for example hospital inpatient, primary care and outpatient department, making it more difficult to capture satisfactorily in epidemiological research. This means there is wide clinical heterogeneity between studies of heart failure, making generalisability difficult[182].

Cause of death in heart failure is generally due to cardiovascular causes. It can be divided into[200]:

- Sudden death due to arrhythmias, about half of deaths[201]. This proportion may be falling due to increasing use of cardiac devices, resulting in more patients dying of progressive heart failure.
- Acute exacerbation, with rapid deterioration in symptoms that fails to respond to medical management [202].
- General deterioration and progressive multi-system failure resulting from systemic effect of illness[7].

There is some evidence that patients with more severe symptoms of heart failure are more likely to die from worsening heart failure, whereas less symptomatic patients are more likely to suffer sudden cardiac death[203, 204].

Although prognostication and a palliative care approach could be important for patients potentially dying from all three modes of death, it could be suggested that the group with more symptoms and progressive heart failure are a particularly important group to identify. Unfortunately most of the studies did not measure primary outcome beyond all-cause mortality. A notable exception was: study 11 which identified: "cardiac death, non-sudden cardiac death and non-cardiac death"[169]. Mode of death can be difficult to determine and prone to bias so a further strength was they were all diagnosed by "standard criteria and decided by independent physicians"[169]. The study did show that an abnormal poincaire plot was

associated with an increased hazard of sudden death, HR 5.3 (CI 1.0-27.5) P<0.05, but the CIs are wide and although do not overlap the null value of 1 are close to it.

3.6.5 **Prognostic indicators recommended in clinical practice**

It could be argued that there is an "art to prognostication"[205], and clinician prediction of survival is important rather than relying on prognostic variables. In cancer patients, clinician prediction of prognosis does not appear to be helpful for survival over six months on its own, although it was suggested it could be used in combination with other variables[120]. As with cancer patients, clinician prediction of survival for heart failure patients is prone to bias and tends to over-estimate survival[190, 206], and again, it is suggested that they should be used in combination with prognostic variables[81].

One study[112] explored a routinely used clinician predication of survival, "the surprise question", in combination with clinical variables, and compared the clinical utilities of sensitivity and specificity with the SHFM. This is the GSF prognostic indicator guide described in **figure 4** of **chapter one**, and represents a relatively simple model. This study by Haga et al[112], demonstrated that GSF prognostic indicator guide, as determined by the HFNS had low specificity, especially in frail elderly, as the HFNS felt that sudden death was very likely in most of these elderly patients.

In comparison, the SHFM is a multi-variable model, with the largest number of variables of the common multi-variable models[197]. As described above, despite its initial derivation from trial data, it has been validated in a large community cohort of patients receiving contemporary heart failure and thus should be more representative of the heart failure population as a whole [192, 196]. It is seen as the "gold standard" for routine prognostication in ambulant heart failure populations[111]. The SHFM, despite appearing to be a more robust prognostic tool, and having a very high specificity for predicting death (99%), had such a low sensitivity (12%) that its clinical utility as a tool to identify people in the last year of life appears to be very poor.

Overall neither the GSF or the SHFM were clinically useful predictors of death in this population of community heart failure patients, seen by HFNS in the UK[111]. Furthermore, the GSF has no published data supporting its accuracy[112].

3.6.6 **Reconsidering the research question?**

The difficulty does not seem to be finding prognostic variables, as there are many proposed. The problem is that many are not validated in unselected patients with heart failure. Moreover, as for both the GSF and the more hopeful SHFM, they may be found to be lacking in accuracy when tested in a population of community heart failure patients in general practice, who are elderly and have multiple co-morbidities[111, 112]. The main focus of this thesis is the identification of patients who may benefit from a palliative care approach rather than whether they are going to die within a particular timeframe. Instead of continued attempts to predict *when* patients will die, proposed prospective research should be conducted to identify *which* patients would benefit from a palliative approach to their care, that is, an assessment of and attention to current needs and symptoms and discussions relating to future aims of care. One study has investigated used the SHFM to assess patients that may benefit from a specialist palliative care team review rather than to predict death. This was a retrospective case note review, with a higher risk of bias than the studies included in the systematic review, but it is an interesting outcome measure[207]. In addition, as discussed in **chapter one**, heart failure patients may have supportive and palliative care needs experienced in the last *few years* of life, not just the last year, which are often overlooked and unmet. A *prognosis* based trigger to identify patients who might benefit from a palliative care approach, aiming to assess and address such needs, would therefore be inadequate and will merely continue the current inequity of access to palliative care by the usual care team and perpetuate the relative lack of timely and appropriate referral to specialist palliative care services.

3.6.7 **Design of future studies regarding prognostication**

Prognostication therefore has limited utility as the primary means whereby heart failure patients are identified as those who may benefit from a palliative care approach. However, it remains an important goal for future research. An estimate of likely survival is important in order to allow patients and carers to be included in discussions and decisions about future care. These discussions form the basis for advance care planning, both for medical advance care planning (for example, device deactivation and determining a ceiling of medical intervention) as well as other issues such as preferred place of care. It is also important, simply because patients

would like to know[19, 208]. Prognostic research regarding the end of life is possible[209]. Lessons for future prognostic research for heart failure patients at the end of life include:

- The selection of appropriate patients, that is, an inception cohort (i.e. those with no, or more practically those with early disease) is considered the gold standard [210]and would reduce the problem found in this review of study selection criteria (such as hospitalisation) then not being able to be used as predicator. This may not always be possible or appropriate in palliative care studies. As a minimum, it should be a well-defined cohort of heart failure patients assembled at a common point in the course of their disease[211].
- The prospective cohort should represent "real life" populations including older patients and those with co-morbidity, to reduce spectrum bias[193]. Ideally, there should be a low rate of non- participant in the cohort, but this is not always possible, particularly in palliative care populations[212].
- It has been suggested that predictors that include measuring change of variables over time may be more useful than single point in time measurements[81, 213]. A few variables in this review were of this type, notably NT-proBNP reduction percentage of <30% during hospitalisation[166] and percentage weight change[181], and these could be targeted for future study.
- Careful consideration is required as to the measured outcomes. Mode of death (for example, sudden or progressive), appropriately defined and preferably independently confirmed may be useful. However, mortality may not be the most important outcome to patients[143] and others such as symptoms or quality of life may be more appropriate. Prognosis is not just about death, but predicting worsening of symptoms or need for additional care support may be useful for both patients and professionals.
- Finally, it has been said that prognostic models are easy to produce, hard to validate, harder still to implement in clinical practice and evidence of impact on decision making is nearly always lacking[143]. The importance of validation of the model or prognostic variable in other populations is vital[198]. However, not only is it necessary for a prognostic tool to be valid, but the effect on clinical practice should be demonstrated[214]. The SUPPORT study discussed in **section 1.6.2** showed that even when clinicians are given

prognostic information they often fail to communicate that to patients or alter their clinical decision making[121]

3.7 Summary

Even with the exclusion of poor quality studies, a plethora of proposed prognostic variables remain. However, these are explored in a single or in only a few studies, often in restricted populations such as trial patients or patients awaiting transplant. Therefore they cannot be generalised to the population as a whole and it is difficult to see how these individual variables could be implemented in daily practice. This systematic review failed to find clinically useful prognostic variables to identify patients in the last year of life. However, it would be useful to identify good predictors of this phase of life in order to allow for patient and carer involvement in advance care planning. This is likely to be an important driver for the UK policy emphasis on prognostication, which has a major aim to reduce hospital admissions at the end of life. Future prognostication research should concentrate on variables measured over time and studying real life populations more representative of patients with advanced heart failure and comorbidity. In **chapter four**, the GPRD study, creatinine will be explored as a prognostic variable, in a real life general practice population.

However, as seen in **chapter one**, patients with heart failure have palliative care needs that are not confined to the last year of life, therefore policy based on prognosis even if there were prognostic predictors that were fit for purpose would miss many patients with palliative care needs. Instead of trying to predict *when* patients will die, the ability to identify *which* patients would benefit from a palliative approach to their care would be a way of breaking down the primary barrier put in place by a trigger for care based on prognosis. This is more in keeping with the WHO definition of palliative care which emphasises the aim of maximising quality of life for patients with a life limiting illness, without fixing this within a defined timeframe. This will be explored further in the qualitative study **chapters five** to **seven.**

4 An exploratory study using General Practice Research Database to compare recognition of palliative care needs for patients with heart failure compared with those with cancer

4.1 Introduction

The systematic literature review in the previous chapter demonstrated a paucity of clinically useful prognostic variables identifying the last year of life. In addition, many of the studies were in restricted populations such as trial patients. The study presented in this chapter uses contemporaneously collected clinical data representative of the UK primary care population to explore whether people with heart failure are identified as needing a palliative care approach and when this occurs. Palliative care registers mainly use prognosis such as the surprise question ("would I be surprised if this patient were still alive in 12 months?') to identify patients who may be eligible for a palliative care approach[39, 40]. Therefore this chapter will investigate the utility of a prognosis based trigger to access palliative care in an unselected population. Patients with cancer were used as a standard comparator as palliative care for patients with cancer is well established in the UK.

4.2 Research aims and objectives

The overall objective of this study is to explore the use of GPRD to compare documented recognition of the need for a palliative care approach by primary care teams, for patients with heart failure, compared with those with cancer. It will explore whether prognostic variables for the last year of life, for patients with heart failure are readily available within GPRD, and if so, whether there is any evidence that these are used to guide the clinical decision for placement on the palliative care register.

The specific aims of the study are to:

1. Identify patients in GPRD practices in England who died in 2009. Identify those who had cancer and/or heart failure, using the Quality and Outcomes Framework (QOF) guidance for being on a cancer or heart failure register[215, 216].

2. Identify within these groups:

i. GP recognition of the need for a palliative care approach. This is measured by the patient being on a palliative care register (another QOF target)[215, 216].

ii. If poor prognostic variables for patients are recorded and if present did they guide the decision for placement on the palliative care register

4.3 Method

4.3.1 General Practice Research Database

The General Practice Research Database (GPRD) is a large well-validated database of anonymised electronic medical records from general practice in the UK[217, 218]. Five million persons are included in the GPRD and demographically it represents the UK population as a whole[219]. In the UK the estimated mid 2009 UK population was 62 million[220] and so GPRD represents about 8% of the UK population. Initially GPRD used data from Vision (one of the general practitioner software systems for recording clinical data), but now uses data from all four main general practitioner electronic health record (EHR)-IT systems, including Vision[221]. Other general practice research databases are available. One example is QResearch which use data from a different general practice computer system, Egton Medical Information Systems (EMIS)[222]. GPRD is the largest validated and most utilised UK primary care database[223]. In the UK patients are registered with one GP or practice who acts as a gatekeeper for referrals to secondary care. The vast majority of health interventions take place in primary care and there is the potential for a lifetime of medical records to be kept in general practice. Therefore GP databases represent a potentially powerful research tool for complete records of contemporaneously collected data. Information found within GPRD includes patient demographic information, clinical information and information about consultations, any medication prescribed in general practice, immunisation history, practice and staff information, referral information and details of any tests requested or carried out in general practice[224]. Clinical information is recorded in Read codes, a coded thesaurus of clinical terms widely used in the NHS especially in general practice[225]. For clinical information and consultations free text information as well as Read codes are available in GPRD[221] but they were not used for this study.

4.3.2 **Ethics**

Following application to GPRD and successful protocol submission to Independent Scientific Advisory Committee (ISAC) for Medicines and Healthcare products Regulatory Agency (MHRA)database research permission for the research was granted (Protocol number: 10_168R). GPRD has obtained ethical approval from a Multi-centre Research Ethics Committee (MREC) for all purely observational research using GPRD data; namely, studies which do not include patient involvement, such as this study. Data released to the student are fully anonymised and free from personal identifiers. ISAC is responsible for reviewing protocols for scientific quality, but may recommend that study-specific MREC approval is sought if ethical issues arise in relation to an individual study, this was not necessary for this application. The data were obtained free of charge under a Medical Research Council (MRC) initiative.

4.3.3 **Initial identification of cases**

The study population was initially defined as:

- Patients that were registered with a GP practice that contributes to the GPRD database in England, approximately 400 GP practices.
- Patients who died during 2009. Estimated date of death was based on the deathdate variable, which is derived using an in-house algorithm by GPRD, to adjust for potentially poor recording of death data.

Eligibility criteria included:

- Patients who were aged 18 or over at the time of death (focus of study is palliative care in adults). GPRD includes year of birth only (for adults), therefore age in years was estimated as (year of death - year of birth).
- Patient who had a minimum of one year up-to-standard (UTS) follow-up prior to date of death (to ensure had sufficient good quality data to allow analysis).UTS follow-up is that which occurs after the data provided by that practice has been declared "up-to-standard", as assessed by GPRD in-house quality metrics.

This data were extracted by GPRD from their records.

4.3.4 **Data management**

These data were obtained on a DVD in the standard GPRD format in text files. These were organised into data files: additional, clinical, consultation, immunisation, patient, practice, referral, staff and test, and look up files for coding schema were also provided. These were transferred to a secure server connected to a password protected university computer. The data was stored in Microsoft Structured Query Language (SQL) Server 2008 database and statistical analysis was performed using Stata version 12.1. All of the files were explored to gain familiarity with the data and dates were reformatted to be used in Stata and/ or SQL as appropriate. Files were linked by the variable patid, an encrypted unique identifier given to each patient in GPRD and sorted by the eventdate variable the date an event or episode was recorded by the GP as occurring. Linkage was carried out in Stata or SQL depending on the size of the data. If in SQL it was linked to Stata for further analysis using an ODBC (Open Database Connectivity) command. In Stata the command merge was used. Linkage in SQL was carried out by Dr Eleanor Kane, Research Fellow, Epidemiology and Cancer Statistics Group, University of York; all other analyses were carried out by the student. Each patid had many rows of data corresponding to different events or episodes of care and so each row needed to be labelled with the variables of interest (e.g. diagnosis, being on the palliative care register) to identify if the other variables were present if the same patid. For counts it was important to count per patid i.e. per patient or case rather than per episode. The rows corresponding to episodes of care for each patid were numerically labelled so that only row number one could be counted.

4.3.5 **Identification of patient groups**

When the term register is used in this thesis it refers to local (individual GP practice) Quality and Outcomes Framework (QOF) registers defined by Read codes and described below, rather than regional registers such as cancer registers[226] or regional palliative care registers, for example, Coordinate my care[227]. Palliative care register is a generic term and many GP practices will use the GSF (see **section1.3***) to coordinate care for palliative care patients and call their palliative care register the GSF register.*

The initial eligible population was identified by GPRD. Search terms for cancer, heart failure and palliative care were developed.

These were identified by determining which patients were on the cancer, heart failure or palliative care registers. These registers are QOF indicators and have defined Read codes. QOF was introduced by the Department of Health in 2004 as a voluntary incentive scheme for GP practices in the UK, rewarding them for how well they care for patients[228]. QOF encourages UK GPs to keep accurate records or registers of patients with specific diseases or health needs. Diseases that are included on QOF registers are selected on the basis that they are able to be clearly defined and diagnosed[215, 216]. The definitions including the appropriate Read codes are defined by a group of primary care academics with an interest in that condition and with extensive consultation with interested groups and are piloted before use[229]. The data from QOF is being used to calculate prevalence data for chronic disease burden in the population and so are robust methods of identifying a disease[230].

4.3.5.1 Palliative care register

For the QOF palliative care register, palliative care is defined as the active total care of patients with life-limiting disease and their families by a multi-professional team. There is an emphasis on palliative care for all patients regardless of diagnosis and being led by primary care teams with input from specialists in palliative care as appropriate. The palliative care register should include all patients in need of palliative care/support.

A patient should be included on the palliative care register if any of the following apply:

1. Their death in the next 12 months can be reasonably predicted (rather than trying to predict, clinicians often find it easier to ask themselves 'the surprise question' –'Would I be surprised if this patient were still alive in 12 months?').
2. They have advanced or irreversible disease and clinical indicators of progressive deterioration and thereby a need for palliative care e.g. they have one core and one disease specific indicator in accordance with the GSF Prognostic Indicators Guidance.
3. They are entitled to a DS 1500 form. The DS 1500 form is designed to speed up the payment of financial benefits and can be issued when a patient is

considered to be approaching the terminal stage of their illness. For these purposes, a patient is considered as terminally ill if they are suffering from a progressive disease and are not expected to live longer than six months[215].

Over 99% of GP practices use a palliative care register[215]. ***Entry on the palliative care registry was used in this study as an indication that a patient was identified as needing a palliative approach to their care.*** The Read codes for being on a palliative care register are detailed in **table 9**.

The decision to put a patient on a palliative care register is made by the primary care team. In order to qualify for the QOF points for using a palliative care register the team need to use at least one of the qualifying diagnostic Read codes for palliative care (see **table 9**) and record this in the individual patient's records. The palliative care QOF has been in place since 2006 and has been widely taken up in practices with over 99% of practices taking part[39].It is unlikely, therefore that patients will be discussed at a palliative care team meeting, another part of the palliative care QOF without ensuring that they are appropriately coded, as this is how the practices are paid for this QOF.

The palliative care register as defined by QOF highlights that is palliative care regardless of diagnosis and in addition, the payment is for prevalence of patients on the palliative care register so practices are incentivised to include as many appropriate patients as possible[39].As discussed in **section 4.5.3** it remains possible that some patients may be recognised as needing a palliative care approach by primary care but not be on a palliative care register or coded using the appropriate Read codes. This is a limitation of analysis of contemporaneously collected data, but because of QOF it is likely that the number of such patients will be small. In addition, being on a palliative care register is an intervention in itself as it allows access to a multidisciplinary team meeting and coordination of care. Therefore, not being on the palliative care register indicates an inequity in care.

4.3.5.2 Heart failure register

Since April 2006, all patients with heart failure should have been included in the heart failure register. All patients with suspected heart failure should be investigated and this is expected to involve, as a minimum, specialist investigation (such as echocardiography or natiuretic peptide assay) and often specialist opinion[215]. The

heart failure register should include all patients with heart failure, including those with heart failure with preserved EF (see **section 1.4**). However, the therapeutic and prognostic benefits of therapy are only proven in those with reduced EF heart failure. Patients with heart failure with preserved EF may, therefore, be under represented in heart failure registers[215, 231].

4.3.5.3 Cancer register

The cancer group is defined by QOF as all patients with a diagnosis of cancer excluding non-melanotic skin cancers[216]. QOF may verify this group by comparing with reported prevalence of cancer[215].

4.3.5.4 Prognostic variables

The systematic literature review (**chapter three**) identified a plethora of prognostic variables associated with being in the last year of life in patients with heart failure. Many of these are variables that are not available within GPRD. Serum creatinine, with a cut off of 140μmol/L had the highest sensitivity and specificity (compare with Seattle Heart Failure Model or GSF) of identifying the last year of life for heart failure patients in a similar population to this study (UK General Practice)[112].

Another important prognostic variable is co or multi-morbidity[194]. This was not identified as a variable in the systematic literature review as trials and transplant waiting lists tend to exclude patients with co-morbidity. The following diseases were included as comorbid conditions: diabetes mellitus (DM), stroke, COPD (Chronic Obstructive Airway Disease) and CKD (Chronic Kidney disease) and all are recorded onto chronic disease registers and defined by QOF[215].

4.3.6 Data analysis

Once the search terms for cancer, heart failure and palliative care were developed using Read codes they were translated into medcodes used in GPRD. The patients were divided into four groups based on if they were coded as being on the heart failure or cancer register or not at any time prior to death. The four groups were "heart failure only"; "cancer only"; "heart failure and cancer" and "other or unidentified diagnoses". Counts of number of patients or cases in each group were calculated. The total number of patients on the palliative care register within each disease group was identified as well as the time from first being coded as on the

palliative register to death. Demographic data (age and sex) were obtained. Age at death was estimated from 2009 (year of death) minus the year of birth, as month of birth is not provided in GPRD.

The record for serum creatinine was found in the data on medical tests file. Those serum creatinine results that were recorded in the last year of life were noted. The search terms for the comorbidities COPD, CKD, DM and stroke were developed and translated in a similar way to those for heart failure and cancer and are defined by QOF[216].

Another way of identifying heart failure patients is by looking at commonly prescribed medication in this patient group, such as loop diuretics[231, 232]. Loop diuretic prescriptions were identified using the productcode variable which links to British National Formulary (BNF) chapter headings and so all loop diuretic prescriptions, including combination preparations were identified.

The medcode 6924 was searched to determine those patients that were coded for "DS15100 completed", Read code 9EB5.00. On the referral file the nhspec variable equal to 27 was searched to determine the number of recorded NHS referrals to palliative medicine.

Sensitivity analysis of the last recorded date of codes being within the year of death, i.e. during 2009 and within five years of death that is during 2005 or later within the heart failure only and cancer only groups were calculated.

The clinical files were searched for entity 149 (cause of death), and then identification of those with a non-zero adid variable. This then linked with the additional file, where information regarding cause of death was found. This was recorded as Read codes and Read terms and as part I (a) I (b) I(c) and II, corresponding to sections of the death certificate. Part I is used to show the immediate cause of death and any underlying cause or causes. Part II should be used for any significant condition or disease that contributed to the death but which is not part of the sequence leading directly to death. In Stata this was converted from "long" that is each cause was on a separate line to "wide" where all the data regarding the cause of death for one patient was on the same line using the reshape

command. This data was exported into an excel spread sheet and categories of cause of death were sorted manually in excel.

These are descriptive data and statistics are reported as absolute numbers or proportions. The time in days from first time coded as on a palliative care register to date of death were also summarised as median and interquartile range.

4.4 Results

4.4.1 Patient groups

4.4.1.1 Initial coding and main counts

A total of 31 667 patients in the database died in 2009 and of these patients 27 689 (87%) had sufficiently complete records to meet the eligibility criteria.

The eligibility criteria required at least a year of records prior to the adult patient's death and that they met GPRD acceptability criteria for the quality of data imputed.

Table 9 contains the search terms for being on the palliative care register using Read Codes defined by Quality and Outcomes Framework (QOF) and translated into medcodes used in GPRD. Cancer and heart failure medcodes were obtained in the same way. Co-morbidly medcodes for DM, stroke, COPD and CKD were similarly developed (**see appendix seven**).

Table 9: Medcodes for being on the palliative care register		
Medcode	Readcode	Readterm
7060	ZV57C00	[V]Palliative care
6664	8BA2.00	Terminal care
6924	9EB5.00	DS 1500 Disability living allowance completed
12739	8CM1.00	On gold standards palliative care framework
18551	8BJ1.00	Palliative treatment
10019	8BAP.00	Specialist palliative care
9755	8H7g.00	Referral to palliative care service
74909	8CM4.00	Liverpool care pathway for the dying
26353	1Z01.00	Terminal illness - late stage
22288	8HH7.00	Referred to community specialist palliative care team
26354	8BAT.00	Specialist palliative care treatment - outpatient
49651	8BAS.00	Specialist palliative care treatment - day care
100607	8CM1000	GSF supportive care stage 1 - advancing disease
100525	8CM1100	GSF supportive care stage 2 - increasing decline

Table 9. Medcodes for being on the palliative care register

Among the eligible patients (n= 27 689), 3 122 (11%) were identified as having heart failure only, 7 608 (27%) as having cancer only and 803 (3%) as having both. Of the 27 689 eligible patients, 5 311 (19%) were identified as being on the palliative care register (**table 10**).

Table 10: Proportion of patients, with each diagnosis, identified as being on the palliative care register		
Diagnosis	Total cases	Total cases on the palliative care register (expressed as % of patients with each diagnosis)
Heart failure only	3 122	234 (7)
Cancer only	7 608	3 669 (48)
Both heart failure and cancer	803	257 (32)
Unidentified or other diagnoses	16 156	1 151(7)

Table 10. Proportion of patients, with each diagnosis, identified as being on the pallitaive care register.

4.4.1.2 Demographic data

Demographic data (age and sex) are illustrated in **tables 11 and 12** for the total population and patients on the palliative care register respectively. The population is generally older with the largest proportion of patients being 80 to 89 years. Cancer patients were younger than heart failure patients. The patients identified as needing a palliative care approach were younger, and notably the cancer group the largest proportion of patients were in the 70 to 79 year age group. Sex ratios were approximately even. Demographic data for gender in heart failure patients tend to show a female predominance, this was not shown in the GPRD population.

Table 11: Demographic data (age and sex) for all cases and for each diagnosis. Percentages may not total 100 due to rounding.					
	Total N (%)	Heart failure only N (%)	Cancer only N (%)	Heart failure and cancer N (%)	Total of all other cases N (%)
Total	27 689 (100)	3 122 (100)	7 608 (100)	803 (100)	16 156 (100)
Sex					
Male	13 311 (48)	1 462 (47)	3 922 (52)	448 (56)	7 479 (46)
Female	14378 (52)	1 660 (53)	3 686 (48)	355 (44)	8 677 (54)
Age in years					
<60	2 805 (10)	87 (3)	854 (11)	11 (1)	1 853 (11)
60 to 69	3 397 (12)	202 (6)	1 492 (20)	57 (7)	1 646 (10)
70 to 79	6 067 (22)	598 (19)	2 173 (29)	190 (24)	3 106 (19)
80 to 89	10 159 (37)	1 382 (44)	2 389 (31)	396 (49)	5 992 (37)
≥90	5 261 (19)	853 (27)	700 (9)	149 (19)	3 559 (22)

Table 11. Demographic data (age and sex) for all cases and for each diagnosis. Percentages may not total 100 due to rounding.

Table 12: Demographic data (age and sex) for all cases on the palliative care register for each diagnosis. Percentages may not total 100 due to rounding.					
	Total N (%)	Heart failure only N (%)	Cancer only N (%)	Heart failure and cancer N (%)	All other cases N (%)
Total	5 311 (100)	234 (100)	3 669 (100)	257 (100)	1 151 (100)
Sex					
Male	2 688 (51)	110 (47)	1 901 (52)	158 (61)	519 (45)
Female	2 623 (49)	124 (53)	1 768 (48)	99 (39)	632 (55)
Age in years					
<60	669 (13)	7 (3)	550 (15)	6 (3)	106 (9)
60 to 69	1 074 (20)	14 (6)	872 (24)	24 (9)	164 (14)
70 to 79	1 480 (28)	44 (19)	1 114 (30)	74 (29)	248 (22)
80 to 89	1 589 (30)	111 (47)	957 (26)	120 (47)	401 (35)
≥90	499 (9)	58 (25)	176 (5)	33 (13)	232 (20)

Table 12. Demographic data (age and sex) for all cases on the palliative care register for each diagnosis. Percentages may not total 100 due to rounding.

4.4.1.3 Timing of entry onto palliative care register prior to death

For each patient on the palliative care register the time from first coding of being on the palliative care register to date of death was calculated and stratified by each diagnosis in **table 13** and illustrated in **figure 9**. Median time on the palliative care register and interquartile ranges are recorded in **table 14**. The heart failure group had a high percentage (29%) of patients identified as needing a palliative approach to their care only in the week prior to their death. This contrasts with the cancer patients where about a third of patients were identified six weeks to six months prior to their death and only eight per cent in the week prior to their death. However, in the heart failure group it was possible to identify patients before six weeks prior to their death despite the concerns expressed in the literature regarding prognostication. There remains 10% of heart failure patients on the palliative care register for over two years. The deaths due to other causes showed a similar pattern to the heart failure group. The heart failure and cancer group showed a pattern that was a mix of the cancer only and the heart failure only groups.

Table 13: Time from first time coded as on a palliative care register to date of death for each disease group. Percentages may not total 100 due to rounding.

Time since palliative care register to death	Heart failure only N (%)	Cancer only N (%)	Heart failure and cancer N (%)	All other cases N (%)	Total (%)
≤ 1 week	69 (29)	294 (8)	30 (12)	299 (26)	692 (13)
> 1 week to 6 weeks	40 (17)	755 (21)	61 (24)	257 (22)	1 113 (21)
> 6 weeks to 6 months	57 (24)	1 193 (33)	60 (23)	284 (24)	1 594 (30)
< 6 months to 1 year	24 (10)	640 (17)	37 (14)	137 (12)	838 (16)
<1 year to 2 years	17 (7)	504 (14)	32 (12)	111 (10)	664 (12)
< 2 years to 5 years	22 (9)	251 (7)	30 (12)	52 (5)	355 (7)
> 5 years	4 (2)	25 (0.7)	6 (2)	6 (1)	41 (1)
Missing	1 (0.4)	7 (0.2)	1 (0.4)	5 (0.4)	14 (0.3)
Total	234 (98.4)	3 669 (100.9)	257 (99.4)	1 151 (100.4)	5 311 (99.3)

Table 13. Time from first time coded as on a palliative care register to date of death for each disease group. Percentages may not total 100 due to rounding.

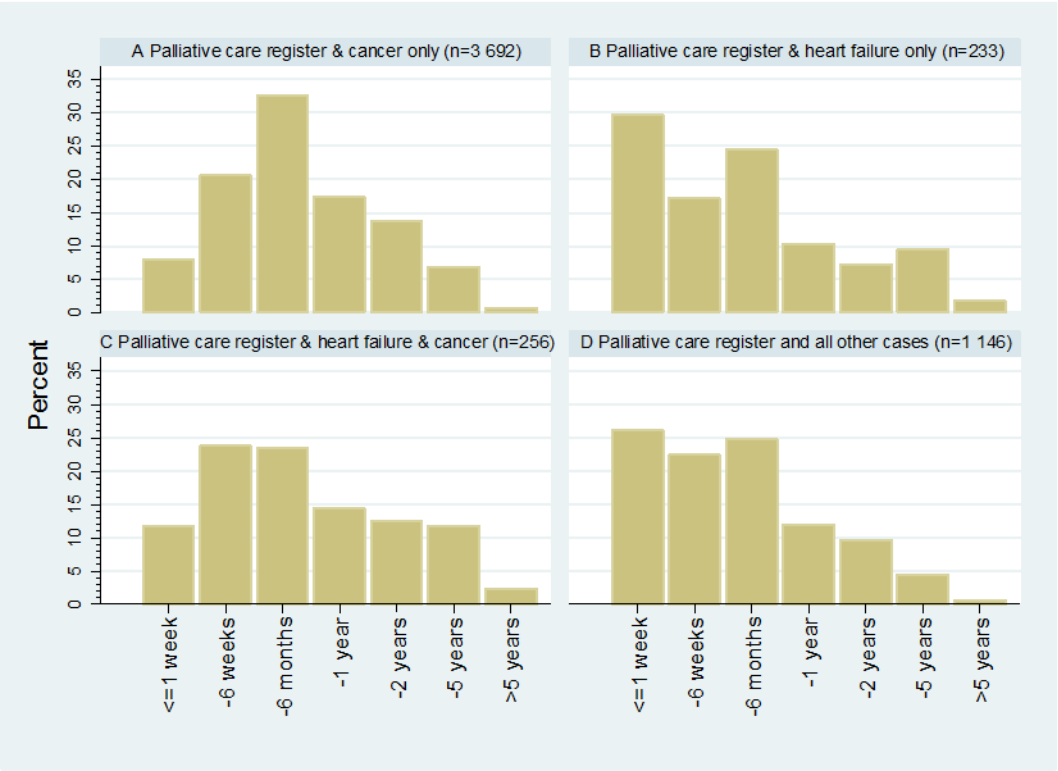

Figure 9. Time from first record on a palliative care register to date of death for each disease group. Missing data is not included.

Table 14: Summary statistics (median and interquartile 25 to 75% range) of time in days from first record on a palliative care register to date of death for each disease group.

Summary statistics	Heart failure only	Cancer only	Heart failure and cancer	All other cases	Total
Median	63	115.5	99.5	47	95
Interquartile range	5-220	36-311	28.5-382	7-196	24-289

Table 14. Summary statistics (median and interquartile 25 to 75% range) of time in days from first record on a palliative care register to date of death for each disease group.

4.4.2 Evidence of prognostic variables of advanced disease in GPRD

4.4.2.1 Serum creatinine, with a cut off of 140µmol/L

Of the 27 689 patients, 25 364 (92%) were identified as having a blood creatinine result available in GPRD. GPRD records blood tests that are requested in primary care, not those that are taken in hospital or in other settings such as private clinics. Seventy per cent (19 352/27 689) of patients had a serum creatinine result in the last year of life and this is displayed by diagnoses and identified need for a palliative care approach in **table 15**. **Table 15** demonstrates that is a commonly recorded

variable in UK general practice and so has potential to be useful as a prognostic variable.

Figures 10 to **12** show the last serum creatinine value in those patients that had a creatinine result in the last year of life, for all patients (**figure 10**) identified as needing a palliative care approach (**figure 11**) and by each diagnosis (**figure 12**). Patients diagnosed with heart failure (**figure 12B**) had a higher percentage of patients with a creatinine level of >140 µmol/L than the other groups (**figure 12A and 12D**). However, the majority of patients with heart failure (**figure 12B**) had a creatinine level that was <140µmol/L in the last year of life.

Overall serum creatinine with a cut off of 140µmol/L was a poor predictor of the last year of life as the majority of all patients who had a creatinine taken in the last year of life had a normal creatinine (cancer only 86%, heart failure 67%, heart failure and cancer 73%, other diagnoses 85%, all deaths 82%). It was also not used to make a decision about the palliative care register as the proportions were similar (cancer only 87%, heart failure only 63%, heart failure and cancer 81%, other diagnoses 86%, all deaths 86%).

Table 15: Number (%) of patients with a creatinine result in the last year of life by diagnoses and identified need for a palliative care approach.

Diagnosis	Total Cases (% with creatinine result)	Palliative care register (% with creatinine result)
Heart failure only **Creatinine in the last year of life**	3 122 **2 589 (83)**	234 **202 (86)**
Cancer only **Creatinine in the last year of life**	7 608 **5 815 (76)**	3 669 **2 882 (79)**
Both heart failure and cancer **Creatinine in the last year of life**	803 **684 (85)**	257 **225 (88)**
Unidentified or other diagnoses **Creatinine in the last year of life**	16 156 **10 264 (64)**	1 151 **8 29 (72)**

Table 15. Number (%) of patients with a creatinine result in the last year of life by diagnoses and identified need for a palliative care approach.

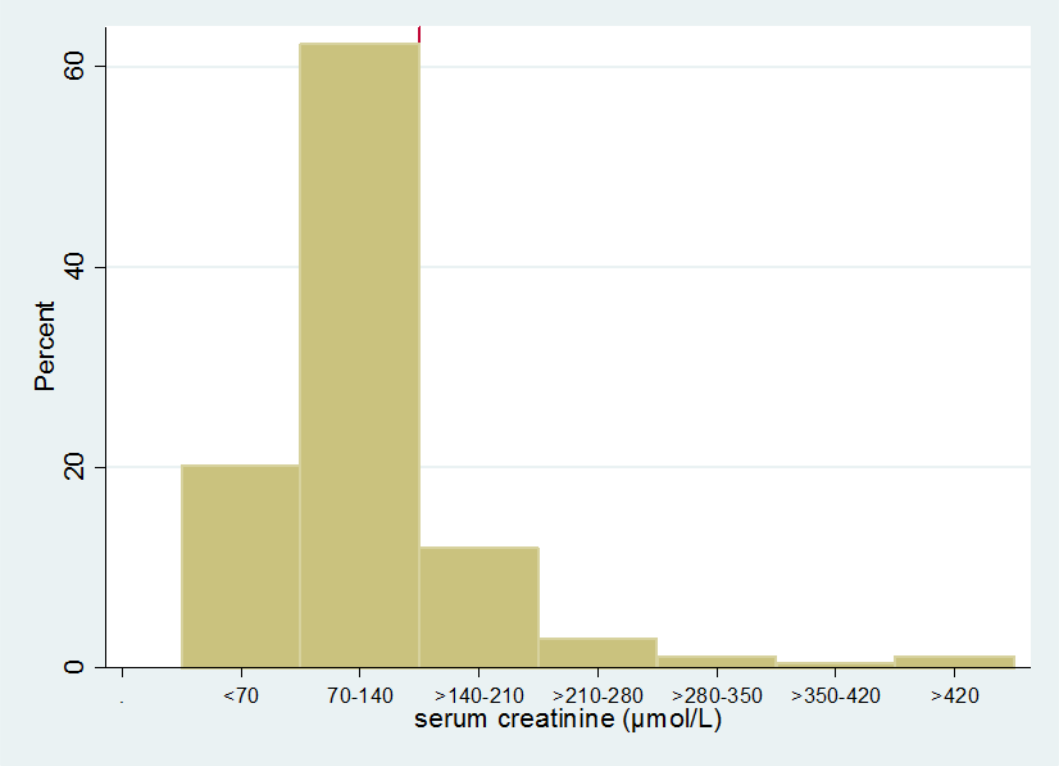

Figure 10. Last recorded serum creatinine level in all patients (n=19 352). Only patients that had a serum creatinine recorded in the last year of life were included. Reference line is creatinine value of 140µmol/L.

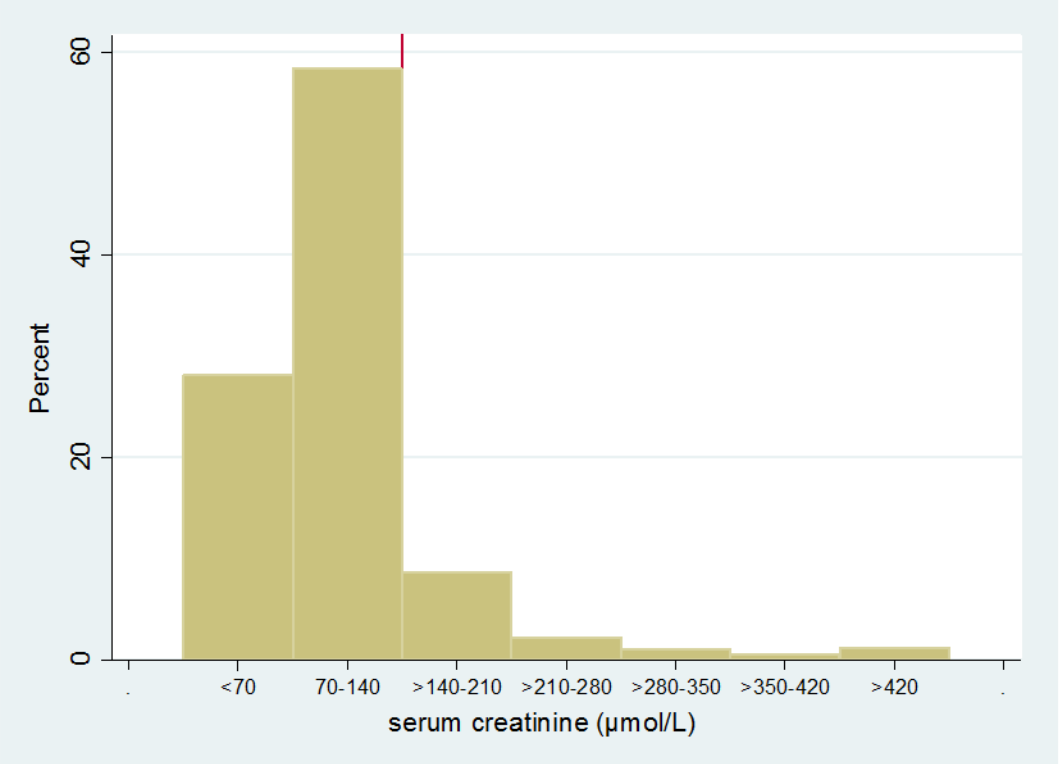

Figure 11. Last recorded serum creatinine level in patients on the palliative care register (n=4 138). Only patients that had a serum creatinine recorded in the last year of life were included. Reference line is creatinine value of 140µmol/L.

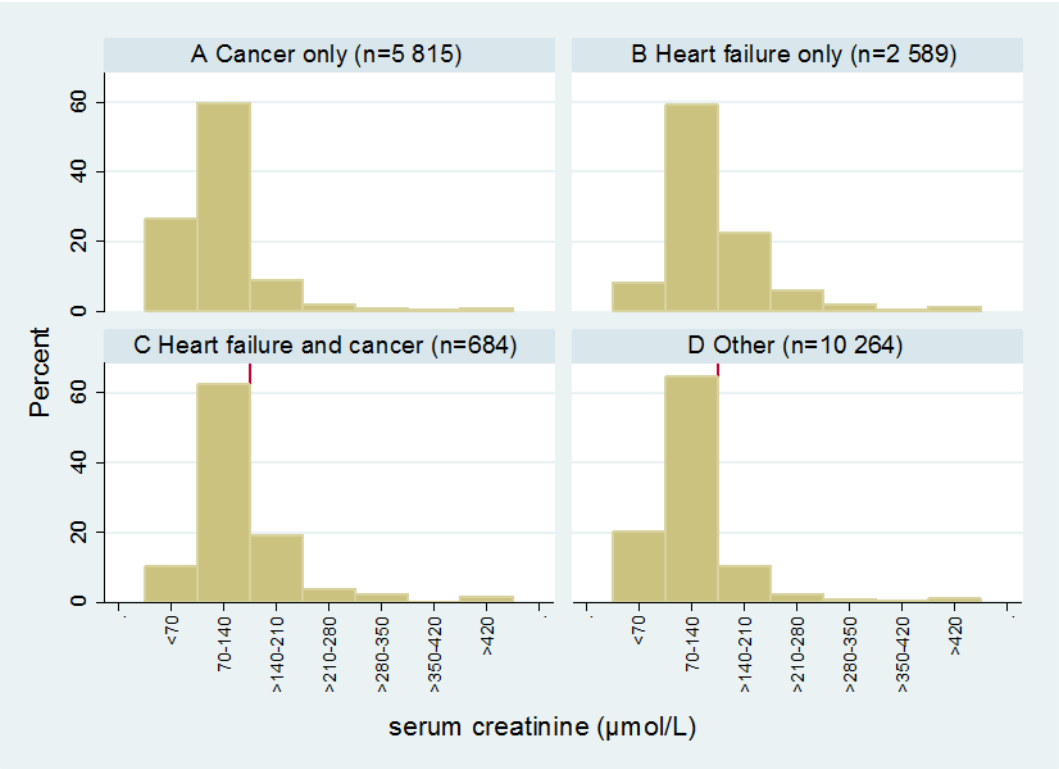

Figure 12. Last recorded serum creatinine level in patients by each diagnosis. Only patients that had a serum creatinine recorded in the last year of life were included. Reference line is creatinine value of 140µmol/L.

4.4.2.2 Co or multi-morbidity

Another potentially important prognostic variable is co or multi-morbidity[194]. The information from the co-morbidities is also useful descriptive data of co-morbidities of a representative sample of heart failure patients in the UK.

Looking at comorbidities of the 27 689 patients 4 740 (17%) had DM, 5050 (18%) had a stroke, 7 537 (27%) had CKD and 3 678 (13%) had COPD. Of the 5 311 patients recognised as needing a palliative care approach 837 (16%) had DM, 681 (13%) had stroke, 1 222 (23%) had CKD and 717 (14%) had COPD. **Table 16** shows the patients with each diagnosis and by identification of need for palliative care approach, showing the numbers with co-morbidities. Co-morbidity was more frequent in the heart failure group (both total cases and those on the palliative care register), most notably with regard to chronic kidney disease. CKD is defined in QOF as stage three to five chronic kidney disease, estimated glomerular filtration rate of less than 60mL/min.

Table 16. Number (%) of patients with comorbidities (DM, stroke, CKD, COPD or all 4) for each diagnosis and for those recognised as needing a palliative care approach.		
Diagnosis	Total Cases (% with comorbidity)	Palliative care register (% with comorbidity)
Heart failure only	**3122**	**234**
and DM	812 (26)	47 (20)
and stroke	741 (24)	57 (24)
and CKD	15 58 (50)	130 (56)
and COPD	603 (19)	51 (22)
Cancer only	**7 608**	**3 669**
and DM	1 136 (15)	544 (15)
and stroke	948 (12)	344 (9)
and CKD	1 637 (22)	695 (19)
and COPD	947 (12)	424 (12)
heart failure and	**803**	**257**
cancer	184 (23)	64 (25)
and DM	160 (20)	42 (16)
and stroke	377 (47)	116 (45)
and CKD	178 (22)	64 (25)
and COPD		
Other diagnoses	**16492**	**1 151**
and DM	2 607 (16)	182 (16)
and stroke	3 200 (19)	238 (21)
and CKD	3 964 (24)	281 (24)
and COPD	1 949 (12)	178 (15)

Table 16. Number (%) of patients with comorbidities (DM, stroke, CKD, COPD or all 4) for each diagnosis and for those recognised as needing a palliative care approach.

4.4.3 Validity of using primary care records

4.4.3.1 Confirming patient groups: heart failure

Loop diuretics were used to identify possible heart failure patients. The number of patients who were ever prescribed a loop diuretic and those that were prescribed a loop diuretic in the last five years were identified. These results were stratified by diagnosis and if they were identified as being on the palliative care register and displayed in **table 17**. Patients diagnosed as having heart failure showed high rates

of loop diuretic prescribing, as expected. Some loop diuretic prescribing such as those from hospital clinics is not recorded on GPRD (but these are unlikely to be many, and would relate to single short periods of prescription as it would be unusual for secondary care to take responsibility for on-going diuretic prescription). The relatively high rates of 32 to 44% of loop diuretic prescriptions in the non-heart failure group could represent patients who have not been formally coded or recognised as having heart failure or use of loop diuretics for other reasons, such as pedal oedema, not just to heart failure.

Table 17. Number (%) of patients prescribed diuretic therapy ever or in the last five years, stratified by diagnosis and identified as needing palliative care approach.

Diagnosis	Total Cases (% with loop diuretic therapy)	Palliative care register (% with loop diuretic therapy)
Heart failure only	**3122**	**234**
Diuretic therapy	2 811 (90)	220 (94)
Diuretic therapy in last five years i.e. 2005 or later	2 739 (88)	219 (94)
Cancer only	**7 608**	**3 669**
Diuretic therapy	2 663 (35)	1222 (33)
Diuretic therapy in last five years i.e. 2005 or later	2 404 (32)	1118 (30)
Heart failure and cancer	**803**	**257**
Diuretic therapy	726 (90)	233 (90)
Diuretic therapy in last five years i.e. 2005 or later	703 (88)	225 (88)
Other diagnoses	**16492**	**1 151**
Diuretic therapy	6492 (39)	512 (44)
Diuretic therapy in last five years i.e. 2005 or later	5859 (35)	478 (42)

Table 17. Number (%) of patients prescribed diuretic therapy ever or in the last five years, stratified by diagnosis and identified as needing palliative care approach.

4.4.3.2 Confirming patient groups: palliative care

Entry on the palliative care registry was used in this study as an indication that a patient was identified as needing a palliative approach to their care. Medcodes for specific aspects of palliative care, DS1500 completion (a possible consequence of the recognition of the need for a palliative care approach) referral to palliative medicine (an example of specialist palliative care) were also investigated.

The specific medcode for "DS 1500 Disability living allowance completed" was searched for but not analysed further due to insufficient numbers of patients (n=7) with this code. Referral data is also available on GPRD and the code "referrals to palliative medicine" was interrogated but again not further analysed as only 41 patients were recorded as being referred to palliative medicine. The small numbers are likely to reflect under recording of both DS1500 and referrals to palliative medicine using these codes and these details are likely to be recorded in the free text. The referral data specifically refers to NHS referrals and so does not include referrals to independent hospices or to non-medical palliative care providers such as specialist nurses. Even despite this there is likely to be significant under recording as Read codes.

4.4.4 **Relevance of diagnosis to death:**

4.4.4.1 Timing of diagnosis

It is difficult to determine if conditions diagnosed in the past are relevant to the patient's death. For example, one patient was coded as having breast cancer in 1955 but as it is recorded that she died in 2009 after being admitted to a nursing home with dementia, the cancer diagnosis was unlikely to be relevant. **Figures 13 and 14** show the distribution of the year of the most recent GP code recorded for heart failure and cancer. The majority of the patients were their condition was recorded recently however one patient had their cancer most recently recorded back in 1951 and one their heart failure most recently in 1960. Sensitivity analyses were carried out for the heart failure only and the cancer only groups. This was to determine if there was a difference in the results if codes that were only recorded more recently were used. The last ever date heart failure or cancer recorded was determined and if it was in 2009 or later i.e. the year of death or if it was in 2005 or later, within five years of the year of death, it was included in the sensitivity analysis.

This was performed for all cases (**table 18**) and all cases where the patient was on the palliative care register (**table 19**).

The proportions of heart failure patients identified as needing a palliative care approach with the one year and five year sensitivity analysis were the same at 8% and very similar to the proportion without the sensitivity analysis at 7%. This suggests that conditions diagnosed in the past remain current in the heart failure group, which fits with the natural history of the disease. In the cancer only group the proportion of patients identified as needing a palliative care approach with the one year and five year sensitivity analysis were similar at 54% and 55% but higher than the proportion without sensitivity analysis which was 48%. This suggests that some of the cancers diagnosed in the past may no longer be relevant. However, this would mean that the proportion of cancer patients identified as needing a palliative care approach may be higher than reported and the inequity between the two groups, in fact, wider.

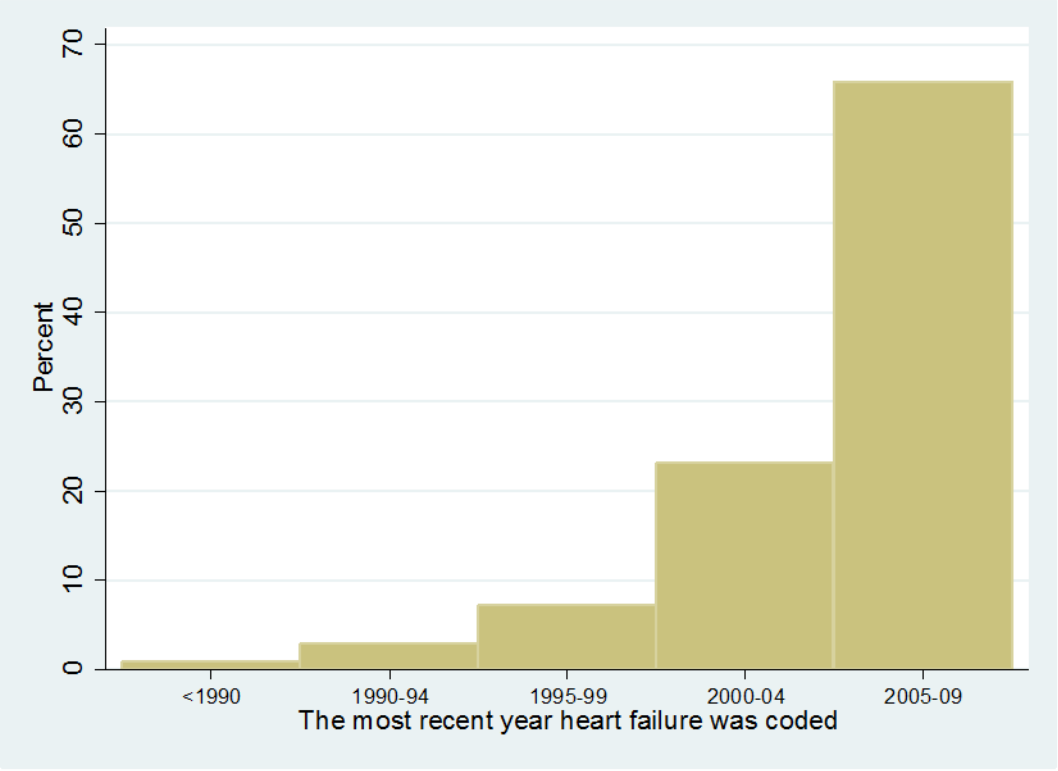

Figure 13. Distribution of patients by the most recent year heart failure was recorded in their GP notes. N=7602 as six records had no date recorded.

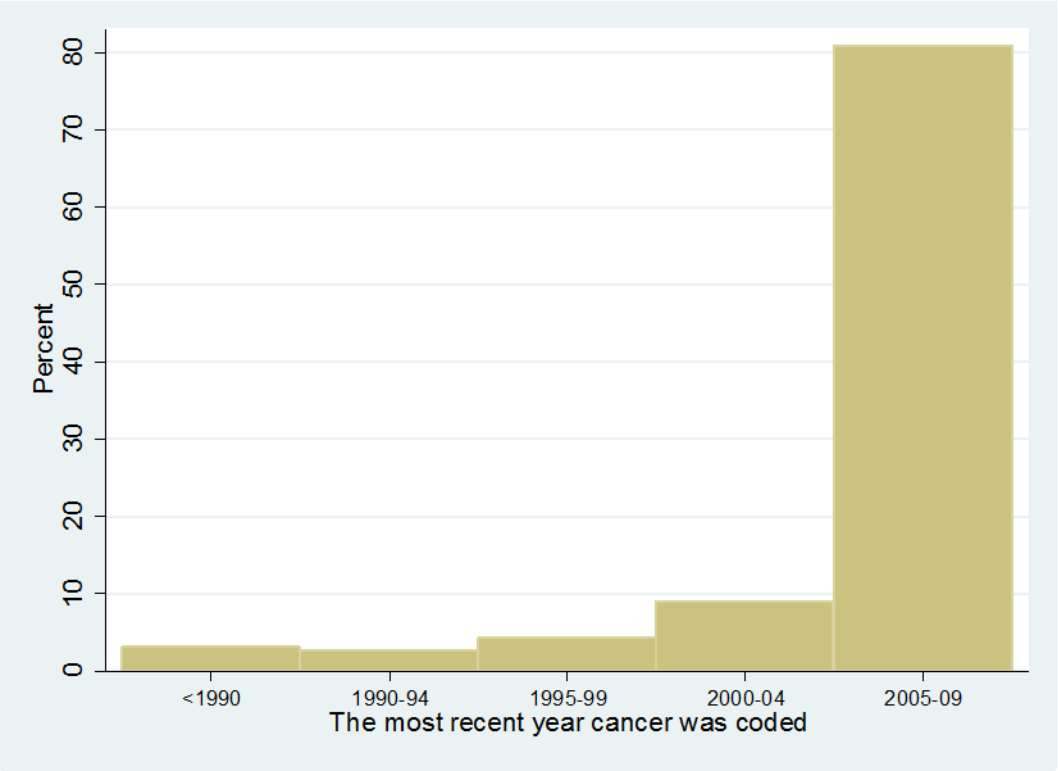

Figure 14. Distribution of patients by the most recent year cancer was coded. N=3 118 as four records had no date recorded.

Table 18. Number of patients included in sensitivity analysis for all cases, for each diagnosis.		
	Heart failure only N	Cancer only N
Sensitivity analysis for last coding recorded in 2009 or later for all cases	1 031	3 462
Sensitivity analysis for last coding recorded in 2005 or later for all cases	2 082	6 267

Table 18. Number of patients included in sensitivity analysis for all cases, for each diagnosis.

Table 19. Sensitivity analysis for all cases on the palliative care register by diagnosis. * This is total number of cases, or total number of cases after sensitivity analysis, values as table 10		
	Heart failure only % (N/total number of cases*)	Cancer only % (N/total number of cases*)
Cases with identified palliative care needs	7 (234/3 122)	48 (3 669/7 608)
Sensitivity analysis for last coding recorded during 2009 for cases with identified palliative care needs	8 (87/1 031)	54 (1 869/3 462)
Sensitivity analysis for last coding recorded during 2005 or later for cases with identified palliative care needs	8 (157/2 082)	55 (3 421/6 267)

Table 19. Sensitivity analysis for all cases on the palliative care register by diagnosis

4.4.4.2 Cause of death as recorded in GPRD

This research is looking at patients who have been identified prior to their death as having cancer or heart failure and then identifying if they were recognised as needing a palliative care approach. This may or may not mean that they died directly of heart failure or cancer. Especially for heart failure, as it cannot be recorded as a cause of death without a further qualifying cause such as ischaemic heart disease and cause of death data do not always identify all patients who had heart failure as a significant illness prior to their death. For all diseases cause of death data may be recorded as pneumonia or similar with no record of contribution of cancer or heart failure. Despite this caveat, it is useful to look at cause of death data in this population. Cause of death data were available for 5644/27 689 (20%) of patients and for 1 198/5 311 (23%) of patients identified as needing a palliative care approach. These are relatively low percentages and may not be representative of the population as a whole, for example it might be more likely to be recorded in certain populations, such as those who died at home. It is not routine for cause of death data to be recorded in GPRD and it is not as robust as national cause of death data which were not available as part of this project. Cause of death as documented in GPRD is tabulated by total and by diagnosis in **table 20** and for all patients on the palliative care register and diagnosis in **table**

21. Despite the caveats discussed the majority of cancer and cardiovascular causes of deaths occurred in the appropriate diagnosis group.

Table 20. GPRD recorded cause of death by diagnosis. Percentages may not total 100 due to rounding.					
Category of cause of death	Total N (%)	Heart failure only N (%)	Cancer only N (%)	Heart failure and cancer N (%)	All other cases N (%)
Cancer	1 536 (27)	10 (1)	**1 290 (78)**	95 (41)	141 (5)
Cardiovascular including peripheral vascular disease and abdominal aneurysm	1 297 (23)	**523 (62)**	77 (5)	88 (38)	609 (21)
Stroke	444 (8)	57 (6)	36 (2)	3 (1)	348 (12)
Dementia and other neurological diseases	463 (8)	41 (5)	27 (2)	4 (2)	391 (13)
Respiratory disease (non-cancer)	348 (6)	59 (7)	46 (3)	12 (5)	231 (8)
Gastro intestinal or liver disease (non-cancer)	231 (4)	26 (3)	19 (1)	-	186 (6)
Renal disease (non-cancer)	146 (3)	16 (2)	25 (2)	6 (3)	99 (3)
Infection (no other underlying cause)	745 (13)	74 (8)	93 (6)	16 (7)	562 (19)
Old age	214 (4)	15 (2)	18 (1)	4 (2)	177 (6)
Other	220 (4)	17 (2)	29 (2)	3 (1)	171 (6)
Total	5 644 (100)	838 (100)	1 660 (102)	231 (100)	2 915 (99)

Table 20. GPRD recorded cause of death by diagnosis. Percentages may not total 100 due to rounding.

Table 21. GPRD recorded cause of death for patients identified as needing a palliative care approach by diagnosis. Percentages may not total 100 due to rounding.					
Category of cause of death	Total N (%)	Heart failure only N (%)	Cancer only N (%)	Heart failure and cancer N (%)	All other cases N (%)
Cancer	865 (72)	1 (2)	**754 (92)**	56 (78)	54 (21)
Cardiovascular including peripheral vascular disease and abdominal aneurysm	65 (5)	**36 (69)**	11 (1)	8 (11)	10 (4)
Stroke	41 (3)	3 (6)	8 (1)	1 (1)	29 (11)
Dementia and other neurological diseases	69 (6)	3 (6)	9 (1)	1 (1)	56 (22)
Respiratory disease (non-cancer)	38 (3)	1 (2)	9 (1)	1 (1)	27 (11)
Gastro intestinal or liver disease (non-cancer)	12 (1)	1 (2)	1 (0.1)	-	10 (4)
Renal disease (non-cancer)	21 (2)	4 (8)	5 (1)	3 (4)	9 (4)
Infection (no other underlying cause)	63 (5)	-	16 (2)	2 (3)	45 (18)
Old age	21 (2)	2 (4)	3 (0.4)	-	17 (7)
Other	2 (0.2)	1 (2)	1 (0.1)	-	-
Total	1 198 (99.2)	52 (101)	817 (99.6)	72 (99)	257 (102)

Table 21. GPRD recorded cause of death for patients identified as needing a palliative care approach by diagnosis. Percentages may not total 100 due to rounding.

4.5 Discussion

4.5.1 **Main findings**

The main findings are as follows:

1. There is gross inequity between the proportion of patients on both cancer and palliative care registers 48% (3 669 of 7 608) compared with only 7% (230 of 3 122) for patients on both heart failure and palliative care registers.
2. More heart failure patients are registered on the palliative care register within the last week of life than those with cancer. With the small number of 230 patients with heart failure that were recorded as needing a palliative approach to their care, 29% were only placed on the palliative care register in the week prior to death compared with 8% of those with cancer.
3. Known markers of poor prognosis do not appear to have influenced the decision for placement on the palliative care register. The suggested prognostic variables (serum creatinine>140 µmol/L and co-morbidity) can be identified in GPRD. However, in line with the systematic literature review (**chapter three**) they were found to have limited clinical usefulness.
4. It is feasible to use this large database to identify the cancer and the heart failure patients and explore recognition of the need for a palliative care approach. This was achieved by using QOF Read codes. It was further confirmed by comparison with prescription data (loop diuretics), sensitivity analysis of the last recorded date the diagnosis was coded and comparison with GPRD recorded cause of death. The section below will compare the data with similar sources in the literature.

4.5.2 **Comparison with other studies**

It is helpful to compare data with other studies, although no data is directly comparable, because of different methods of coding and different populations.

Twenty seven thousand six hundred and eighty nine patients were included in this study. Three thousand one hundred and twenty two patients (11%) were identified as having heart failure only, 7 608 (27%) as having cancer only and 803 (3%) as having both. This was compared with known data regarding cause of death in general practice in a year. Number of patients per practice, based on a study of one small GP practice is 13 patients with cancer and six patients with heart failure[86] and

another source suggests the average GP practice has 100 deaths per year, 25 due to cancer, 33 due to organ failure[233] (not just heart failure but COPD etc..) therefore perhaps 18 due to heart failure. In another study in Scotland looking at six GP practices 30% of patients died from cancer and 20% from organ failure, but these figures did not include sudden death[234]. These proportions are similar to this GPRD study but these studies are based on small numbers of patients.

National data are available from the National End of Life Care Intelligence Network. This network uses data from the Office of National Statistics central death registration of all deaths in England, which is death certificate information. Diseases are coded using ICD10 codes and heart failure is coded within the category "chronic coronary heart disease", which includes heart failure, angina and other chronic ischaemic heart diseases as the underlying cause of death, "the disease or injury that initiated the train of events directly linked to death". In 2009, the same year as this study, 14% (148 771/454 891) deaths were due to chronic coronary heart disease and 29% (131 267/454 891) due to cancer. Although they used a different coding system and classification system the proportions are similar to this GPRD study. The proportions stratified by sex for the years 2004 to 2011 were male 52% (235 095/ 455 449) and 48% female (220 354/ 455 449) in the National End of Life Care Intelligence Network[52]. This would fit with expected patterns showing a slight tendency towards more deaths due to heart failure among men than women and similar disorders. However, the GPRD data in this study showed a slightly higher proportion of female deaths due to heart failure. The age of the participants in this GPRD study is older, including a higher proportion over 80 years than the National End of Life Care Intelligence Network patients. The National End of Life Care Intelligence Network includes information on age of patients who died from 2004 to 2011 and includes patients under 18. Eight per cent (38 906/512 255) of patients who died from chronic coronary heart disease were under 60, 11% (248/512 255) were 60 to 69 and 23% (117 544/512 255) were 70 to 79 and 59% (300 557/ 512 255) were over 60 years. The slight difference in age profile with the GPRD heart failure group being older than the national population who died may also explain the discrepancy in sex distribution between the GPRD population and the national death certificate data, as in older populations there will

be a higher proportion of women, or it could just be due to the differences in coding of heart failure.

The first ever national (England) snapshot of end of life care in primary care was undertaken in 2009. Five hundred and two general practices took part from nine of the ten strategic health authority regions. Practices used an online "After Death Analysis" (ADA) tool to provide anonymised information about all deaths that took place between February and March 2009. Records were provided for 4487 people. Sixty per cent of eligible practices provided information (502 of the 874 invited) and available data covered about half of all deaths during February and March 2009 in the 15 participating PCT areas. Among participating practices, 27% of all deaths were included on the palliative care register and 71% of people on the register had cancer yet just 28% of people dying had a primary diagnosis of cancer. The proportion of patients on the register was higher than in this GPRD study but the practices selected to take part in the audit and it was not designed to be representative of all practices. It is possible that practices who took part were more engaged with palliative care registers. This study also considered the time patients were on the register prior to death: 6% were on for less than one week before death; 10% one to two weeks before death; 7% two to four weeks before death; 46% one to six months before death; 27% more than six months before ; and 5% had no data[235]. This meant that the GPRD data had more patients on the register for more than six months (36%), and more patients on the register for less than a week (13%), which again is likely to reflect differences in the type of practices in the after death analysis audit than GPRD data.

Another study of six GP practices in Scotland showed that of deaths in a six month period, 29% were on palliative care registers and like these GPRD data, fewer deaths due to chronic diseases (20%) were on the palliative care register than patients who died from cancer (68%). The study noted a wide variance in the proportion of patients who were on the palliative care register by practice from 10% to 38%. There is likely to be similar variation in this GPRD study, although this was not examined in this analysis. Patients in the six practices in Scotland were on the register for an average of 13 weeks (median 10 weeks but the range was large from two days to four years)[234].

Serum creatinine>140 μmol/L was identified in the systematic review (**chapter three**) as an appropriate prognostic marker to explore in GPRD[112]. There were high proportions of serum creatinine results recorded in GPRD in the last year of life suggesting it is a marker that was possible to investigate. However, the majority of patients were not above the threshold and GPs did not use this as measure to discriminate if a patient was to go on a palliative care register as patients were still mostly below threshold too. Similarly, multi-morbidity could be successfully identified within GPRD but was not a good prognostic marker. This fits with the conclusions of the systematic review (**chapter three**) regarding the value of prognostic markers. Neither appears to have been used by GPs to inform the clinical decision of placement on the palliative care register.

The data on multi-morbidity is important in its own right as descriptive data regarding the proportions of different diseases present in a UK population of patients with heart failure in their last year of life. Comparing this with known data is difficult as this is scarce and clearly the prevalence is also dependent on other population variables such as age. Data on proportions of CKD in patients with chronic heart failure are difficult to obtain, but it has been suggested that up to 55% of patients with heart failure have evidence of CKD stages three to five[236]. As with CKD the prevalence of COPD in heart failure populations is difficult to determine and a review has showed wide prevalence rate from 8% to 52%[237]. Published data including all deaths in England in 2008 from chronic coronary heart disease, which includes chronic heart failure demonstrates that 23% of deaths were associated with comorbidity with diabetes mellitus[52]. A 1994 cohort of Medicare patients with heart failure in the US identified 29% of patients had had a stroke or transient ischaemic attack[238]. The increased prevalence of stroke in patients with heart failure is likely due to common risk factors and treatment of these patients has resulted in declining rates of stroke in heart failure populations[239]. The other important factor for the multi-morbidity data is that it highlights the high prevalence of multi-morbidity in this population. Differing from selected populations, such as trial participants, patients with heart failure often have other diseases along with their heart failure. The idea of a single disease model and guidelines associated with one disease are not appropriate in this population. The palliative care needs will be associated with the heart failure but also the other diseases and other factors

associated with older age, such as frailty, dementia and social isolation as well as wider psychosocial and spiritual concerns at the end of life. This is beginning to be recognised in the literature[194, 213].

It is possible to identify further heart failure patients in individual practices by searching for loop diuretics and then if appropriate investigating for heart failure[231]. Two research teams are currently undertaking such research, but there is limited published data. It is suggested that it is possible to add up to 20% more patients to the heart failure register by this method. This includes patients with heart failure and reduced EF as well as heart failure with preserved EF and right sided heart failure secondary to chronic respiratory disease[240]. This could explain some of the loop diuretic prescribing in the non-heart failure patient groups; although it could also be due to loop diuretic prescribing for non-heart failure reasons. If as suggested, GPs are failing to diagnose some patients with heart failure, this requires further enquiry but is outside the scope of this study and at the moment there is not sufficient published data to support this view.

This GPRD research examines the patients who have been identified prior to their death as having cancer or heart failure and who have also been recognised as needing a palliative care approach prior to death. This may or may not mean that they died directly of heart failure or cancer. For all diseases cause of death data may be recorded as pneumonia or similar with no record of contribution of cancer or heart failure[241, 242]. Despite these caveats there was a reasonable agreement between disease group prior to death and GP recorded cause of death (**table 20 and 21**). Other sources of cause of death data outside of GPRD include linkage with Office for National Statistics death certification data. This would be more complete than GP recording on cause of death data and may be more accurate. It would be easier to classify as it could be sorted based on ICD 10 classification. However, death certificate or cause of death data should not be used to identify cases for a study like this. Death certification would still have difficulties of inaccuracies described above. Furthermore, the principle of this study was to identify patients who were recognised as having cancer or heart failure prior to their death by their GP and then to explore which were also recognised as needing a palliative approach to their care. If death certificate data had been used it may be

could have identified patients who there was no possibility of the GP recognising the need for a palliative care approach, for example, they were admitted to hospital where they would have been diagnosed and died of their condition (heart failure or cancer) with no involvement of their GP.

4.5.3 **Strengths and limitations**

This is the first study of its kind using a national GP database to study recognition of the need for palliative care and variables of poor prognosis. Routine datasets are currently under-utilised in end-of-life research[243]. The main search terms are well-defined by QOF thus increasing the confidence that the recording is accurate, and likely to be complete or near complete by many GPs. This study had the strength of a very large population-based sample drawn from general practices throughout England. The system of health care in the UK is such that the 99% of the population are registered with a general practitioner[230]. GPRD constitutes contemporaneously collected data .The use of routinely collected data has the advantage that it is not collected for the study, so is representative of actual practice and is not biased by knowledge of the study, especially as it is unselected for the factors of interest. It was known that the patients had died but it was not known if they would be recognised as needing a palliative care approach prior to the study. The patients had the identified diseases and then could be prospectively followed, which is more true to life than retrospectively looking back with cause of death data. However, it has resulted in the denominator being overestimated as it included some who did not die with or of the disease.

The limitations of the study is that it is reliant on the data recorded and coded in GP notes and it is difficult to verify that the information is accurately recorded, or that is recorded using the Read Codes. This is quality-controlled by internal checks by individual GP practices and checked by GPRD that data are "up to standard" and has also been externally validated, to show it is representative of the wider population[217, 218]. The accuracy for this study has been improved by the main search terms being defined by QOF, increasing accuracy and completeness[215, 216]. The other variables explored are clearly defined and available in the database such as gender, age, date of event, blood results or prescription data. The limitations of cause of death data as recorded in GPRD is discussed in **section 4.5.2**. There is always the possibility that recognition of the need for a palliative care approach is

acknowledged by GPs, but that it is it not recorded or coded in such a way as to be recognised in the GP notes, the registers or the computerised record held on the database. By comparing two groups, it is expected that the numbers of patients like this will be similar in each group. This is a complex area, however, and this is an exploratory study with limitations of the data recorded by GPs. Other areas of interest will be explored elsewhere in the research project. For example, the reasons why heart failure patients are or are not placed on the palliative care register and the differences it makes to their care.

4.5.4 **Potential future research**

This was an exploratory study to see if a UK GP database could be used to explore recognition of the need for a palliative care approach in cancer and heart failure. A successful method, using QOF disease registers and Read codes, has been developed to accurately identify the patient groups of interest using GPRD. COPD patients can be similarly identified. It is noteworthy that the unidentified or other diagnoses group were as poorly recognised as being on the palliative care register as the heart failure group. COPD is a common disorder with an incidence of 2.0 per 1000 patient-years in a UK community population[244]. Patients with COPD have unmet palliative care needs, which are comparable to those of cancer patients[245-247]. They have significant symptom burden, poor quality of life, lack of opportunity to make plans for their future care and poor support for their carers[248-251]. Barriers to a palliative care approach include difficulty in prognostication and failure of clinicians to initiate discussions about end of life care[251, 252]. International and national guidance recommend a palliative approach in advanced disease[32, 253, 254]. It would be important to identify if, as with heart failure, there is a discrepancy between GPs recognising the need for a palliative care approach among patients with COPD compared to those with cancer.

Another area of interest would be to explore the data recorded around the time a patient was recognised as needing a palliative care approach such as test results, medication, number of GP contacts and any patterns in the data leading to recognition of palliative care needs. This would be to determine if there are specific variables associated with identification of a trigger to consider the need for a palliative care approach. It would also be interesting to see if recognition of the

need for a palliative care approach in general practice changed over time by analysing later years.

GPRD has now been re-named as Clinical Practice Research Datalink **(**CPRD). It is now a combination of MHRA's GPRD and the Department of Health's National Institute for Health Research (NIHR) Research Capability Programme. This allows linkage to Office for National Statistic central mortality data, Hospital Episode Statistics and other registers such as the Cancer Registry[221, 223].This will allow comparison of codes with death certificate data and/ or cancer registry or hospital records. Other information of interest could be obtained such as place of death, allowing comparison between disease groups as well as those recognised as needing a palliative care approach prior to their death to explore if it influenced place of death. Other outcomes such as patterns of secondary care such as numbers of admissions and days in hospital in the year prior to death could also be explored.

4.5.5 **Implications for practice**

This study does not give information regarding place of death. There is considerable national interest in this although the appropriateness of this as measure of quality of care is contested[20, 255-257]. The National End of Life Care Intelligence Network data on cardiovascular death discussed earlier gives a breakdown of place of death for all deaths in 2004 to 2010 due to heart failure and compared with cancer. The figures are given in **section 1.6.1** and demonstrates that the inequity between cancer and heart failure is not just in general practice recognising the need for palliative care approach but in place of death[105].

4.6 Summary

As far as the student is aware this is the first successful demonstration of the use of a UK primary care database to investigate palliative care questions. The QOF Read codes were robust search terms and could be used in future studies. The database was also successfully interrogated to explore prognostic variables, although in line with the systematic literature review, they did not appear to be clinically useful and these data seem to show that they are not used by clinicians to identify the need for a palliative approach to care. The stark finding is that despite more than a decade of national policy the recommendation to improve access to palliative care for patients with heart failure appears to have been almost totally neglected. As

well as consequences for patients and their families, it will have implications for planning services and considering appropriate place of care.

5 Methodology for qualitative study

5.1 Introduction

Chapter four has highlighted the gross inequities between the recognition of a palliative care approach in general practice between patients with heart failure and those with cancer. However, some patients had been recognised as needing a palliative care approach earlier in their disease trajectory, with a few being on the palliative care register for more than a year. These data are not able to provide an understanding or the reasons for that observation, nor inform about the individual patient's experiences of the transition to a palliative care approach and the consequence of that transition. Therefore, a different research design is required to address these questions and a qualitative approach will be used. Transition in palliative care is defined in **section 1.6.1**.

In this chapter (**chapter five**) the research aims and objectives will be described. The methodology will be discussed; including the theoretical framework for the study and justification for the specific research method used for the qualitative study. Findings of the qualitative study will follow in **chapter six**.

5.2 Research question, aims and objectives

5.2.1 **Research question**

What are the perceptions of patients with advanced heart failure, their carers and health care professionals (HCPs) regarding the transition to a palliative approach to care; and what is the effect on their subsequent experience of advanced heart failure?

5.2.2 **Research aims and objectives**

The aims and objectives are to:

- Obtain individual patients' perspective regarding the transition to a palliative care approach in advanced heart failure by exploring their experience of the transition to a palliative care approach.
- Explore the carers' and HCPs' personal perspective and their perception of the patients' experience of the transition to a palliative care approach.

- Determine the barriers to the recognition and implementation of a palliative care approach in patients with advanced heart failure and understand how these were overcome.
- Explore the effects of the palliative care approach on patients and carers and their experience of the management of their condition.
- Integrate these findings with the systematic literature review and GPRD study to gain further understanding of a palliative approach to care for community based patients with advanced heart failure: recognition of need, transitions in care and impact on patients, carers and clinicians.

5.3 Theoretical framework

5.3.1 **Grand theory**

The overarching or grand theories to consider with respect to this project are epistemological considerations regarding the study of knowledge and ontological considerations of beliefs regarding the nature of reality. The traditional divide in qualitative and quantitative research is seen by some as between constructionism and positivism, although this is contested[258, 259]. Positivism is described as the "scientific method" with objectivity, hypothesis testing and search for truth[260].

Constructionism views reality as socially constructed by our individual, social, and historical contexts and so there is no one absolute shared truth[258]. Another theoretical framework is post modernism, which questions all achievements of modernity (humanism, reason, science and so on) and at its extreme questions all forms of reality to the point of nihilism[261]. This is a simplistic overview and there are variations, differences and overlap between these theories.

The student's personal viewpoint is that HCPs are used to thinking and practising in a world where knowledge is contested. HCPs may be "taught" that the gold standard is the meta-analysis of RCTs but practice in a reality where the trials are often not available or applicable to the patient they see in the clinic. HCPs may also recognise the complexity of the patient they see in clinical practice, beyond the simple biological into psychosocial and spiritual, individual and subjective. It is an old adage that medicine as much an art as a science[153]. Others have recognised the similarities between skills of an interviewer for qualitative research with medical history taking[262] and similarly the effectiveness of case presentations to influence

practice[263, 264]. However, in the uncertain arena of daily clinical practice, there may be an attraction to the positivist viewpoint as it can give clarity in decision-making. Many HCPs may never have previously considered the nature of knowledge. When considering this issue, the student, was struck by a quote from a Yorkshire GP, Dr Read in response to a debate in the British Medical Journal regarding the theoretical thinking behind qualitative research:

> *"I have been subject to this insistence that I must choose my paradigm (and it had better be constructivism)"*[265].

By this quote, Read implies that qualitative researchers are asked to consider their epistemological and ontological perspective but that their answer has to be based on constructivism and needs to reject positivism.

She argues, as do many others that the theoretical divide between the two types of research is not as wide as was traditionally thought[258]. Qualitative and quantitative research do not need to be seen as competing philosophies but can be seen as different items in the "toolkit" of research methods, appropriate for answering different sorts of questions[258]. In general, quantitative research focuses on "what?" and "how much?" questions, and qualitative research "why?" and "how?"[260]. This pragmatism is attractive and has been followed in this thesis as demonstrated by the range of research methods selected. It may also be seen as appropriate when exploring a complex idea such as a palliative approach to care.

The central idea of constructivism is that there is not one truth but multiple subjective realities. This thesis is not seeking to find "the truth" about a palliative care approach in heart failure but individuals' perspectives and experiences which are shaped by their prior experiences and understanding. If one is using the pragmatic approach, it might not be seen as important as in this approach it is the research question that decides the type of research method: quantitative or qualitative. As perspectives are being explored qualitative methods are appropriate for this type of question. The student perceives, however, that it is important that the readers have an understanding of how she thinks about reality, as it affects every step of the research process. If the student had a positivist perspective she would be seeking to eliminate bias at every stage of the study as it would obscure

the single objective truth. As it is, the student recognises and embraces the multiple perspectives and seeks to explore and interpret them rather than eliminate them. An important perspective is that of the researcher herself, "the researcher as research instrument", instead of seeking to eliminate the student's perspective, she recognises and is sensitive to the influence she has on the research using a process called reflexivity (see **section 7.4**)[260].

5.3.2 **Mid-range theory**

Mid-range theories are seen as important in qualitative research[259]. These theories provide conceptual understanding of complex topics and provide a "lens" through which to look at the data and provide a framework for analysis[259]. There is no one correct theory for analysing any specific data and indeed multiple perspectives or "lenses" may be used, the important feature is transparency. Many qualitative researchers perceive that the integration of theory into research is what differentiates qualitative research from anecdotes or journalism[259]. There has been some criticism of the language of qualitative research with its "isms" and lack of plain English and that the language can be used to hide the lack of substance in a specific research project[266, 267]. This is also described by Silverman as "highfalutin theory" and the "emperor's new clothes"[268]. Theory can also mean ***the research literature relating to the topic*** rather than a specific mid-range theory, which is an approach that will be followed in this thesis[269].

The mid-range theory or "lens" used in this research is the philosophy of care known as palliative care. This is a collection of ideas, theories and philosophies rather than one framework and is described in **section 1.2.1 and 1.2.2**. This is also influenced by the student's background as a palliative care doctor. One of the supervisors is a palliative care doctor and researcher and the other supervisor is a GP with a clinical and research interest in palliative care. The student will reflect on the limitations of this "lens" by the process of reflexivity and transparency, explored further in **chapter seven**.

One reason why one specific theoretical framework has not been used in the thesis is that they can be interpreted too rigidly and the reality is more complex. The specific frameworks are useful to provide the conceptual understanding of a complex topic, but the broader framework of the palliative care approach, captures

more aspects of the topic. For example, "The stages of grief" originally described by Dr Kubler-Ross study of terminally patients are not discrete stages but aspects of a single underlying psychological construct – grief[270]. Similarly the descriptions of "closed awareness, suspected awareness, mutual pretence and open awareness" described by Glaser and Strauss[22] are not linear and dying patients can hold multiple awareness contexts simultaneously and dual track approaches such as "hope for the best, and prepare for the worst" may be helpful[126].

The theoretical underpinning of a palliative care approach and the background of the researchers has clearly influenced the research beyond that of a "lens" for data analysis. It has been a fundamental part of the decision to study this research area and the research question itself. It has also influenced access to patients, sampling strategy and the conduct of the interviews. It has also influenced the interpretation and the dissemination of the research.

5.4 Discussion of methodology

Qualitative studies are an appropriate method for the exploration of perceptions which is a key part of the question. Furthermore, there is a need to go beyond the quantification or numbers of **chapter four** to explore in-depth, a small number of specific individual's perceptions, thus generating rich descriptions not possible using quantitative methods. The strength of qualitative research is in its "closeness to the truth", its ability to touch the core of what is going on as opposed to quantitative methods that may only skim the surface[271]. There are no previous studies with this group of patients so a method that allows more freedom with data collection to generate potentially new themes is beneficial.

Semi -structured interviews were selected as the method of data collection. There is criticism of the automatic use of semi -structured interviews as a means of data collection in health sciences[267] and so it is important to reflect on the method of data collection selected. Others criticise interview studies because they use "manufactured data", rather than using naturally occurring data. All methods of data collection have their limitations. Interviews may be generated for the research project but an alternative perspective is that they are expressions of how individuals construct social reality rather than social reality per se. This makes them no less valid as a tool of data collection but they need to be interpreted in this light[272]. This

is where the research question is important. It is about the participants' perceptions of the transition to a palliative care approach to management (recognising multiple subjective realities) rather than one objective truth about an event. It is important to consider what may influence participants' articulation of their perceptions as this is a limitation of the study. This includes issues such as the interaction between the participant and the interviewer, for example if the research participants know if the interviewer is a doctor and this is discussed further in **section 7.4**. Despite interviews being generated data, in this study the participants describe their own experiences using their own words, and so may be seen as more "true to life" than other methods of data collection such as a structured survey or a quality of life score.

Other forms of data collection were considered. Observation research, is still intrusive, and has it limits ethically and practically. In this project with limited patient population it would be difficult to capture sufficient observation data to answer the research question. Similarly, pre-existing data such as documentary sources like diaries or policy documents[273] were not appropriate to answer the research question.

A specific research question was developed from gaps in the research literature consequently a totally exploratory approach using a completely unstructured interview would not have been appropriate. A semi-structured interview method allows for exploration of the research question but allows for new themes to emerge that were not considered or known prior to the interview. Focus groups were not considered appropriate for patient and carers in this research as they require interaction between participants who may have different levels of understanding of the nature of the illness and differences in their wish to explore end of life issues. For HCPs interviews were preferred as they were discussing an individual patient and so focus groups would be less useful. Additional focus groups with HCPs discussing more general aspects of the research question were undertaken but not included in this thesis and will be reported elsewhere.

An additional methodological consideration was the use of multi-perspective interviews (patient, carer and HCP). This was used because it had the potential to provide richer understanding of needs and experiences than interviews with just

one group of participants, such as patients[67, 274]. It is suggested that it is particularly useful for studies about needs of patients, carers and professionals and might provide practical recommendations about how to improve services[274]. The method used was to recruit a patient and ask them to nominate a carer and HCP that they felt were important in their care. This was to ensure the most relevant people were interviewed. It meant that for the HCPs the student had little control over which type of professionals were recruited, for example how many GPS, cardiologists, HFNS or other professional groups.

Purposive or theoretical sampling is a common sampling strategy in qualitative research. The researcher selects participants to represent the beliefs or experiences that the researcher believes will be relevant to the research question rather than a representative sample of the population[260]. In this research, heart failure patients with a palliative approach to their management were specifically sampled. This is a fundamental and novel part of the research question that these patients are interviewed rather than a representative sample of patients with heart failure. By this purposive sampling it will be possible to explore the transition to a palliative care approach in more detail than previous studies, identifying how barriers to the palliative approach were overcome, what difficulties still remain and more importantly the consequence of this transition for the patient and their carers, both positive and negative.

5.5 How the study was conducted

5.5.1 Ethical review and research governance

The study was approved by the National Research Ethics Service Committee Yorkshire and the Humber – Leeds East, REC reference: 11/YH/0344 on 22 November 2011.

Individual Research and Development approval was obtained for each of the NHS sites and also for the three independent hospices.

The protocol was reviewed by the North and East Yorkshire and Northern Lincolnshire Consumer Research Panel and informal peer review was provided by Professor Karl Atkin, Department of Health Sciences, University of York and

Professor Patrick Stone, Professor of Palliative Medicine at St George's, University of London.

5.5.2 **Participants**

The research took place in the community covering the primary care trusts of North Yorkshire and York and Hull. This area includes a mix of urban and rural areas and wide variation in deprivation scores (**see figure 15**).

Scarborough has an integrated heart failure palliative care service[98, 275]. The other HFNS, GP and consultant teams have access to specialist palliative care services, such as day hospice by patient referral.

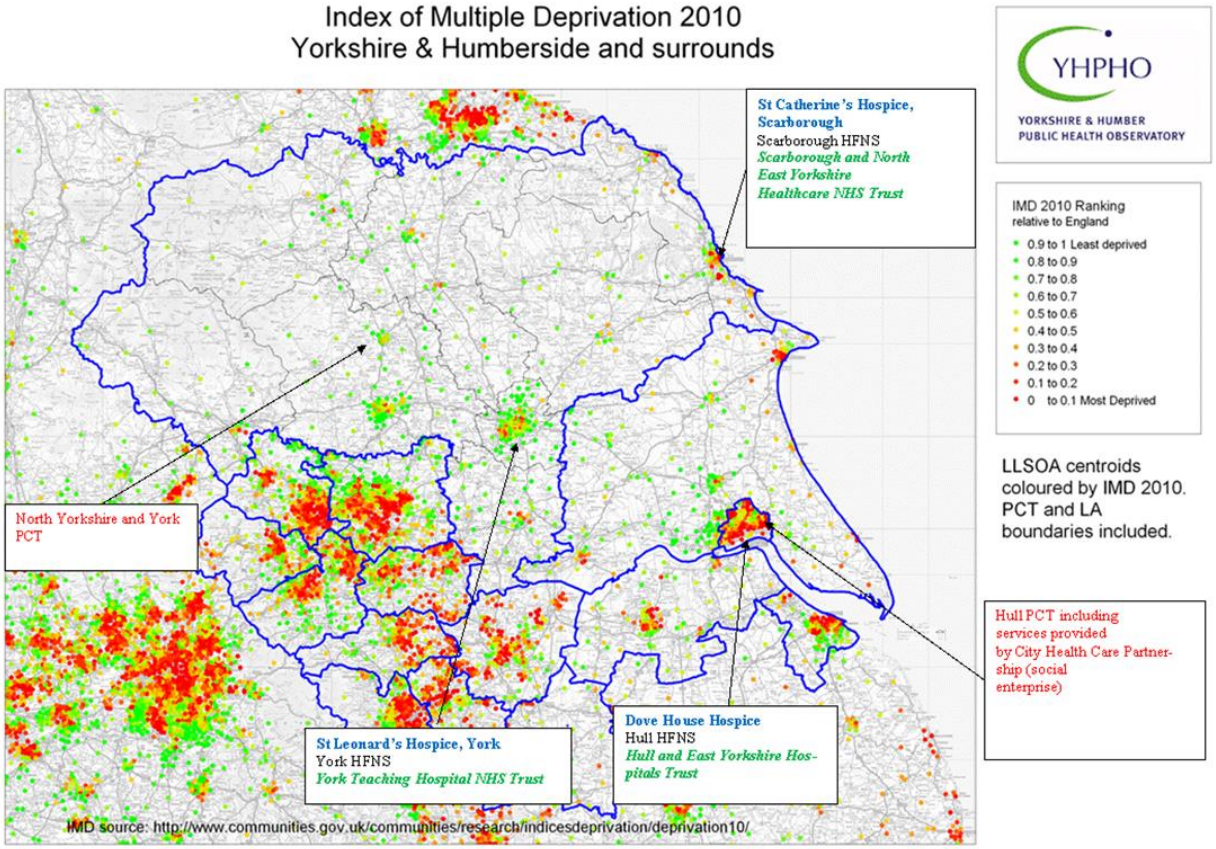

Figure 15. Map of geographical area of research project covering the community of North Yorkshire and York PCT and Hull PCT. The three hospices in the research project are shown in blue, the three centres for the HFNS in black and the acute trusts in green. The deprivation data is from the Yorkshire and Humber Health Intelligence Network[276]

Patients were identified and first approached by:

- HFNS based in Hull, York and Scarborough
- General Practitioners in North Yorkshire and York PCT, Hull PCT and City Health Care Partnership (Hull based social enterprise) who agreed to take part in the study
- HCPs in specialist palliative care services in Hull or Scarborough (St Catherine's Hospice, Scarborough, St Leonard's Hospice, York and Dove House, Hull)

The purpose of this strategy was to identify and recruit patients who were known primarily to the HFNS, specialist palliative care staff or GPs, to maximise variation, rather than recruiting via one type of team. In practice, however, there is close collaboration between all three groups of HCPs.

Patients with advanced heart failure where it had been recognised by the recruiting HCP that a palliative approach to management had been implemented were approached. This may mean the patient had been:

i) put on a general practice palliative care register
ii) had a DS1500 completed (form completed by a clinician when patient has a limited prognosis to allow fast track to certain benefits)
iii) had been referred for specialist palliative care services
iv) or any evidence of advance care planning, such as resuscitation status or preferred place of care

A broad definition of palliative care was used "the palliative approach to care" as discussed in **section 2.6**.

In addition, the patient needed to have had conversation(s) with a HCP regarding the stage of their illness: that cure or full control of their symptoms was unlikely to be possible. In addition, the conversation(s) should have included that there was a change in the focus of their care to help minimise the impact of their symptoms and offering more support to them and their family.

The plan was to recruit equal numbers of males and females. Heart failure is mainly a disease of older people so there was no sampling strategy based on age.

Patients were asked to identify who, if anyone was their main carer and if they thought they would be interested in taking part in the research study. If they preferred the patient and their carer were interviewed together. This is discussed further in **section 7.5.**

Patients were asked to identify the key HCP(s) involved in their care. This may or may not have been the person who asked them about the study.

The main inclusion criteria for patients, carers and HCPs are included in **table 22**. The main exclusion criteria were if the participant was unable or unwilling to provide informed consent or participate in an audio recorded semi-structured interview.

Table 22. Main inclusion criteria for participants in the qualitative study

Patient	Carer	HCP
Adult (>18 years), with advanced heart failure who have been identified by their HCP as having a palliative approach to management Be aware of the stage of their illness; that cure or full control of their symptoms is unlikely to be possible and that there is a change in the focus of their care to helping minimise the impact of their symptoms and offering more support to them and their family Conversation(s) with HCP(s) regarding point above	Adult (>18 years), who have been identified by patients as their carer(s) Able to give informed consent. If unable to give written consent this will be witnessed by an independent person Able to participate in an up to sixty minute semi-structured audio-recorded interview Able to understand and communicate in English in order to participate in the interview without a translator	Adult (over 18 years old), HCP and working for North Yorkshire and York PCT, Hull PCT, Scarborough and North East Yorkshire Healthcare NHS Trust, Hull and East Yorkshire Hospitals Trust, York Teaching Hospital NHS Foundation Trust, City Health Care Partnership St Catherine's Hospice, Scarborough, St Leonard's Hospice, York or Dove House, Hull Able to give written informed consent Able to participate in semi-structured audio-

Table 22. Main inclusion criteria for participants in the qualitative study		
Patient	Carer	HCP
Able to give informed consent. If unable to give written consent this will be witnessed by a carer or member of the usual care team. Able to participate in an up to sixty minute semi-structured audio-recorded interview Able to understand and communicate in English in order to participate in the interview without a translator		recorded interview

Table 22. Main inclusion criteria for participants in the qualitative study

Sample size was determined by data saturation. Data saturation is when data is collected and analysed until no new major themes occur[277]. It was planned that up to 20 patient interviews should be sufficient to allow saturation of themes by qualitative analysis, using the experiences of qualitative researchers outlined by Green and colleagues[278]. The interviews took place from December 2011 to September 2012.

5.5.3 **Data collection**

Demographic data were collected from the participants at the time of interview. Patient data were supplemented with information from their medical record (GP, HFNS or hospice) if possible. These data included recording if the patient was on a palliative care register, other evidence of advance care planning, specialist palliative care involvement, DS1500 completion other evidence of palliative care services, approximate number of GP contacts in the last year and number of hospital admissions in the last year. The student assessed each patient's Karnofsky performance status[279] and the New York Heart Association (NYHA) functional classification system[280] at the time of interview.

Topic guides were used by the student as a framework for the semi-structured interviews (see **appendix ten**). The topic guides were produced to explore areas that the research team considered were important to patient, carers and HCPs (from their experiences, user review and the literature). When appropriate, new issues that arose from earlier interviews were incorporated into subsequent interviews. This included rephrasing questions about advice to other patients in the same situation as them, probing HCPs about patients who had stabilised or lived for many years with a palliative approach and questioning them about why there might be a difference between the number of heart failure patients and cancer patients on palliative care registers (results of GPRD study).The interviews were audio-recorded and professionally transcribed. Contemporaneous notes (field notes) of any particular items of importance, conduct of the interview and physical characteristics not likely to be identified by voice alone were made by the interviewer. Both the audio recorded interview transcript and notes taken regarding the conduct of the interview were analysed together.

5.5.4 **Analysis**

The approach to analysis taken began with the initial coding and a coding framework that were based on the original accounts rather than pre-existing literature or theories. This was important as a strength of the study is that is based on participants' accounts. Qualitative data analysis requires that decisions are made about describing, presenting and interpreting the data as findings. These decisions were based on the coding framework but then were also influenced by the research objectives and interpreted both within the context of the participants accounts and the wider research literature described in **chapter one**.

The student became very familiar with all the transcripts both by conducting the interviews and reading and rereading the transcripts. Two patient interviews and one joint patient carer interview were independently coded by detailed line by line analysis[281] by the student and her two supervisors who met to discuss their coding and agree a draft coding framework. The student and one supervisor (MJ) repeated the process with a further patient transcript and two carer transcripts and finalised the patient and carer coding framework (**figure 17**). The patient framework was initially developed and then modified to include codes that were specific to carers, but as many codes were similar (and for joint interviews the patients and carers

were analysed and coded together) the same coding framework was used for both patient and carer analysis.

The HCP coding framework was developed after the patient coding and independently of the patient transcripts. However, insights gained from developing the patient coding framework were incorporated leading to some similarities between the two coding frameworks. Four HCP transcripts were selected for detailed line by line analysis[281] conducted independently by the student and one supervisor (UM). They met to finalise an initial coding framework. A further four transcripts were analysed independently by the same two researchers using the coding framework and a final framework was finalised by consensus between the two researchers (**figure 18**). The transcripts were selected for multiple coding for variation in types of participants, for example different professional roles and variation in transcript content. All transcripts of patient, joint patient and carer, carer only and HCP transcripts were then re-analysed using the two coding framework but also noting other codes not on the coding framework. A summary of each transcript was also recorded as a memo along with any additional comments from conducting and analysing the transcript. This was important as it meant analysis was not just constant comparison between transcripts but also within each transcript. Therefore constant comparison included comparison both between and within transcripts.

Constant comparison of these initial codes led to the development of categories which formed the main themes[281]. These were developed separately for the patient and carer and HCP group.

The multi-perspective interviews added an additional layer of complexity to the analysis. Joint carer and patient interviews were analysed together rather than separating patient and carer responses. This was done because it is important to analyse transcripts in the context in which they are generated[274]. Analysis of the interaction between the patient and the carer using a similar method to that used in focus group analysis also revealed additional findings[282]. The coding frameworks were linked across individual triads (patient, carer and HCP) or dyads (patient and HCP) to create a coding matrix. From this matrix it was possible to demonstrate similarities or differences or missing information across the different triads and

dyads. Case studies of triads and dyads are shown in the findings as well as thematic analysis across patient, carer and HCP groups. An important part of multi-perspective interviewing is to explore similarities, differences and silences between the different perspectives, i.e. patient, carer and HCP groups[274].

NVivo, SQL version 9 was used to store, organise and sort the data. It was used for coding once the coding frameworks were finalised. Anonymised verbatim quotes are used in the findings to illustrate particular themes, as appropriate.

5.6 Summary

The method of the qualitative study has been outlined in this chapter. The overarching theoretical framework is constructivism and the mid-range theory is the philosophy of care known as palliative care. The research questions for the qualitative study are: what are the perceptions of patients with advanced heart failure, their carers and HCPs regarding the transition to a palliative approach to care; and what is the effect on their subsequent experience of advanced heart failure? Semi-structured interviews were used with patients who were recognised as having a palliative care approach to their care. An important part of the recruitment and subsequent thematic analysis is the multi-perspective approach where the patient nominated a carer and a key health care professional. The next chapter will present the findings of this study.

6 Findings of qualitative study

6.1 Introduction

As described in **chapter five** a multi perspective approach to data collection and analysis was conducted. This resulted in rich data from a variety of interviews.

This chapter will present the findings of the qualitative study, with description of participants and the five main themes .The chapter will conclude with a summary of how far the research aims and objectives have been answered. Strengths and limitations of the qualitative study will be discussed in **chapter seven** and suggested future research in **chapter eight**.

6.2 Participant demographics

The flow of progress of potential patient participants and reasons for exclusion from the study is summarised in **figure 16**. Recruitment continued until data saturation was reached (see **section 5.4**). Saturation was reached after 19 patient interviews as no new findings were emerging from the patient interviews. In particular, there was no new data to add to the coding framework or contribute to answering the research question. Data saturation was led by the patient interviews as they were the primary source of data but this did mean that sufficient sampling was not achieved in all areas of data collection notably with variety of HCPs and geographical region. This is discussed further in **chapter seven**. The plan was to recruit equal numbers of males and females. This was not possible and more men were recruited, possibly reflecting the demographics of heart failure being more common in males.

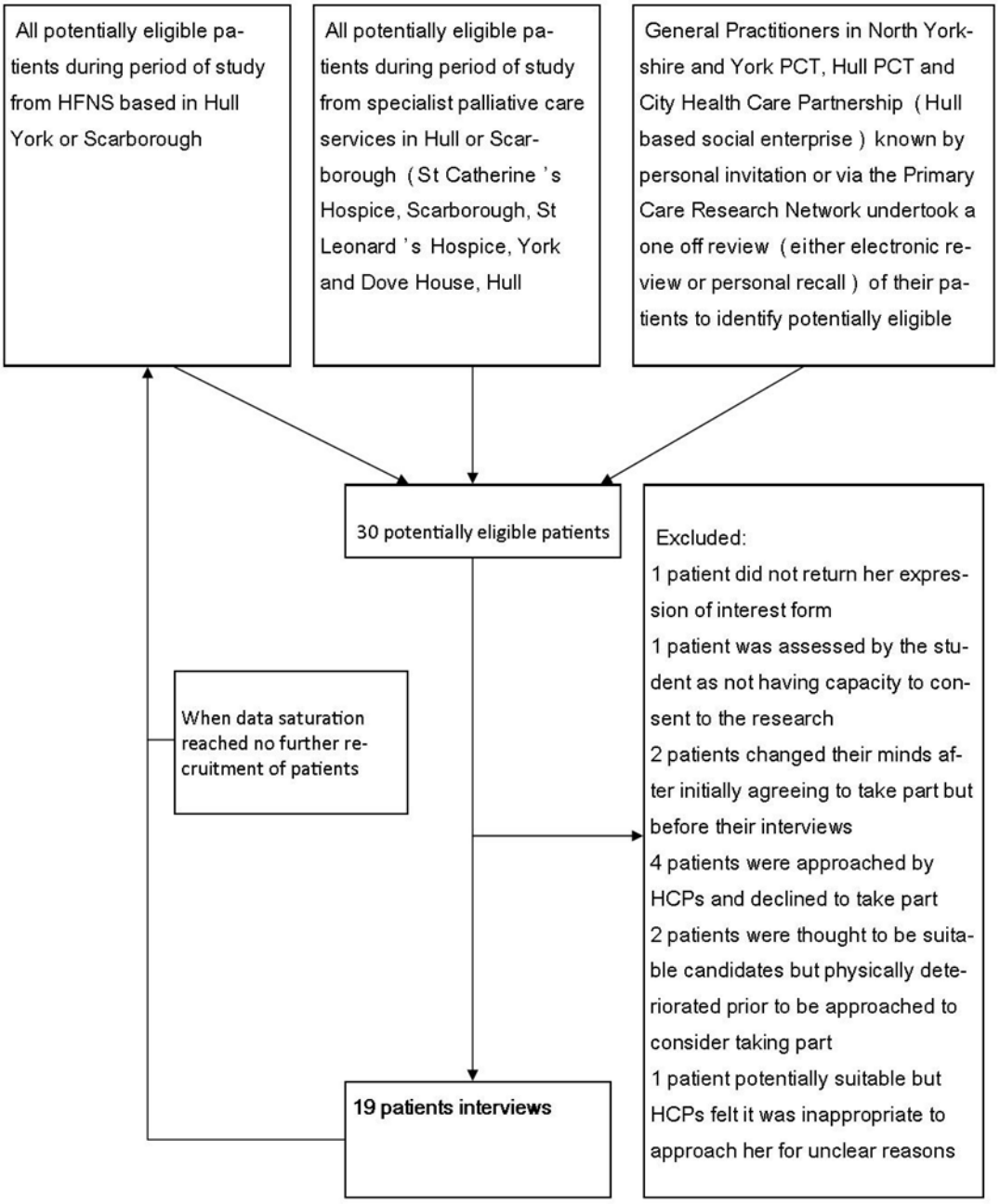

Figure 16. Flow of potential patient participants through the study

19 patients were interviewed:

- Seven single interviews (four female, three male)
- Three separate carer interviews (two female, one male) all grown up children
- Nine husband (all patients) and wife joint interviews (one interview wife present but not participant in research project, therefore responses not used).

Joint or separate carer interview was decided by patient preference. Patient (either single or joint with carer) interviews lasted between 28 minutes and 1 hour 12 minutes. Separate family carer interviews lasted between 22 minutes and 51 minutes. Ethnicity of patients and carers was collected but as they were all White British / White Other it is not included in the tables. Nine patients were from Scarborough, five from York, three from Hull and two from Harrogate. Further demographic information regarding the patient participants are found in **table 23 and 24**.

Table 23: Patient demographic data

Patient number	Age Range	Sex	Palliative care register	Other advance care planning	Specialist palliative care	DS1500
1	60-69	M	Yes	DNAR	Inpatient hospice	Yes
2	50-59	M	No but special access alert on GP records	DNAR	Day hospice	Yes
3	90-99	M	No	DNAR	Day hospice	No
4	60-69	F	Yes	Unknown	Day hospice	No
5	90-99	F	Yes	PPC/ DNAR/	OPD	Yes
6	80-89	F	Yes	PPC/ DNAR	Day hospice	Yes
7	70- 79	M	Yes	No	No	no
8	80-89	M	Unknown	No	Day hospice	Yes
9	80-89	M	Yes	No	Day hospice Macmillan	Yes

Table 23: Patient demographic data						
Patient number	Age Range	Sex	Palliative care register	Other advance care planning	Specialist palliative care	DS1500
					nurse	
10	80-89	F	No	No	Day hospice	No
11	80-89	M	Yes	No	Day hospice	No
12	60-69	F	Yes	DNAR/PPC	Day hospice	Yes
13	80-89	M	Yes	DNAR/PPC	Inpatient hospice	No
14	80-89	F	Yes	No	No	No
15	50-59	M	Yes	No	Now discharged from day hospice	Yes
16	70-79	M	No	No	No	No
17	70-79	F	Yes	No	Day hospice and inpatient hospice Macmillan nurse	Yes
18	80-89	F	No	Unknown	Day hospice	Yes
19	80-89	M	Yes	PPC not DNAR	Inpatient hospice and OPD	Yes

Table 23. Patient demographic data. All the palliative care registers were individual practice based; there are no regional palliative care registers

Key: DNAR=do not attempt resuscitation; PPC=preferred priorities for care ; OPD=out patient department

Table 24. Further patient demographic data						
Patient number	Approxim-ate number of GP contacts in the last year	Number of hospital admissions in the last year	Karnofsky perform-ance status[279]	NYHA[280]	Who recruited	Where interviewed
1	5	4	20	4	Palliative medicine consultant	Hospice inpatient
2	12	0	50	3 /4	Day	Day

Table 24. Further patient demographic data						
Patient number	Approxim-ate number of GP contacts in the last year	Number of hospital admissions in the last year	Karnofsky perform-ance status[279]	NYHA[280]	Who recruited	Where interviewed
					hospice	Hospice
3	3-4	0	60	3 /4	Day hospice	Home
4	12	0	70	3	Day hospice and HFNS	Home
5	5	4	60	3	Palliative medicine consultant	Home
6	3	0	50	3	HFNS	Home
7	10	1	60	3	HFNS	Home
8	4	2	50	3	HFNS	Home
9	6	1	60	3 /4	HFNS	Home
10	3	1	60	3	HFNS	Home
11	3	0	70	2	HFNS	Home
12	unknown	0	60	3	HFNS	Day hospice
13	3	1	50	3	HFNS	Home
14	24	2	50	3	GP	Home
15	10	0	60	2	Gp	Home
16	6	1	70	2/ 3	Nurse practitioner	Home
17	6	3	60	3	Hospice doctor	Hospice inpatient
18	12	2	60	3	Day hospice	Home
19	6	4	50	3 /4	HFNS	Home

Table 24. Further patient demographic data

Carers were identified and approached by the patient. Carer information including information regarding carers who did not take part are shown in **table 25.**

Most carer participants were retired and had held a range of jobs including in health care (nurse and health care assistant); clerical (secretary, accounts manager, postmaster) catering (butcher, tea lady and school cook) and a university lecturer.

Table 25: Carer demographic data						
Patient number	Single/ joint interview	Relationship to patient	How long known patient	Age Range	Sex	Where interviewed
1	No details collected; wife interviewed at the same time as patient					
2	No interview; reason given wife shy					
3	Single	Son	60-69	60-69	M	Their home
4	Single	Daughter	40-49	40-49	F	Relatives home (but separate room)
5	Single	Daughter	60-69	60-69	F	Their home
6	No interview; friend said no					
7	Joint	Wife	58	70-79	F	Their home
8	Joint	Wife	64	80-89	F	Their home
9	Joint	Wife	64	70-79	F	Their home
10	Daughter in law no response, many family bereavements					
11	Joint	Wife	66	80-89	F	Their home
12	Information sheet left for friend; not returned					
13	Joint	Wife	Missing	80-89	F	Their home
14	Family abroad; no other carers					
15	Information sheet left for wife; not returned					
16	Joint	Wife	Missing	60-69	F	Their home
17	Information sheet left for daughter; not returned					
18	No suitable carer					
19	Wife present for interview; but did not want to take part in research					

Table 25. Carer demographic data

14 HCPs were interviewed:

- Some HCPs were interviewed about more than one patient
- Five GP, four HFNS, three specialist palliative care professionals, district nurse and nurse practitioner (primary care)
- Five male and nine female HCPs
- Eight worked in Scarborough, two in York, three in Hull and one in Harrogate

One GP declined due to workload pressures due to staffing issues and so patient 14 had no corresponding HCP interview. One GP had retired but the HFNS was

interviewed instead as nominated as second choice by the patient. All GPs were GP principals. Specialist palliative care professionals included two day hospice nurses and a community nurse specialist. It was an experienced group of professionals who had worked as HCPs for between 16 and 41 years, mean 27 years. HCP interviews lasted between 15 minutes and 44 minutes. Further information about HCPs is detailed in **table 26.**

Table 26: HCP information		
Identity code	Patients interviewed regarding	Did they recruit patient(s)?
GP1	1	No
GP2	2	No
GP3	3	No
GP4	4	No
GP5	15	Yes
HFNS1	5,6	Yes
HFNS2	7,8,9	Yes
HFNS3	10, 11	Yes
HFNS4	13	Yes
SPCP1	12	No
SPCP2	17	No
SPCP3	18	Yes
Nurse practitioner (primary care)	16	Yes
District Nurse	19	No

Table 26. HCP information. Note for patient 14 there was no HCP interview and some HFNS were interviewed about more than one patient. SPCP= specialist palliative care professional

6.3 Coding frameworks and example triads and dyads

6.3.1 Coding frameworks

Separate coding frameworks for patient and carer and HCPs were developed, as described in **section 5.5.4** and are summarised in **figures 17 and 18**.

- Understanding
- Communication
- Health literacy
- Future
- Death /dying
- Experiences: (Of hospital, specialists, HFNS, Primary Care, Hospice including day hospice, emergency services)
- Inter-professional working
- Symptoms/ Comorbidities /QOL
- Spirituality/ personhood
- Family
- Non-professional support
- Community/ neighbourhood
- Social isolation/ loneliness/ social factors
- Management of illness,
- Disease course including varying disease trajectory and acute episodes
- Unmet/unexpressed need
- Other

Figure 17. Summary of patient and carers coding framework. QOL = quality of life

- Decision making
- Individual professionals approach to care
- Disease course
- Prognosis
- Comparison with cancer
- Gold standards framework or palliative care registers
- Services including voluntary and paid carers
- Interdisciplinary care
- Professional roles (hospital specialists, HFNS, Primary Care, Hospice including day hospice, emergency services)
- Management of HF
- Symptoms and QOL
- Unmet need
- Other

Figure 18. Summary of health care professionals coding framework

6.3.2 Three case studies

As discussed in **section 5.5.4** an important aspect of the analysis is that there are multiple perspective interviews as triads (patient, carer and HCP) or dyads (patients and HCP). Three case studies of patient 1 (patient 1 and wife joint interview and GP1); patient 3 (patient 3, separate interview with son and GP3) and patient 11 (patient and SPCP1) are presented in this section as example cases.

6.3.2.1 Patient 1: example of patient and carer differences

Patient 1 was a gentleman in his sixties, who was interviewed in the hospice, where he was an inpatient. He was interviewed with his wife. He had a poor Karnofsky performance status and died a few weeks later at the hospice. Despite his poor performance status he was very keen to be involved in the research as was his wife.

It was a revealing interview, which contributed to theme development. They both described a very difficult period, prior to admission to the hospice where the patient was very symptomatic. They were very grateful for the support of the hospice. They were very aware of the poor prognosis the patient had, and had been aware of this for many years and were accepting of it. What his wife found very distressing almost to the point of anger was that she had not realised how ill he would be prior to death and her anger stemmed from the fact that none of the HCPs had told her about this phase. She had thought and prepared herself for him dying in his sleep and she felt comfortable with that.

Analysis of the interaction between the patient and his wife revealed tensions at times. When his wife was supplying details about how he was referred in he interrupted stating:

> *"Doesn't matter who contacted who love, we're not having a game of chess here."* (Patient 1)

This is contrast with other patient and carer interviews such as patient 7 and 11 where the patient and carer, encourage each other, finish each other sentences to such a degree that it is difficult to demonstrate separate views.

His GP who was interviewed a few months later (due to delays in research approvals in the PCT) revealed additional information. He spoke more about the difficulty at home had been worse for his wife than even for the patient:

> *"I know his wife was actually, in the end, very happy that he did die in the hospice rather than at home, cos she, she said that she'd probably have had to move if she did, but…*
>
> *Well she'd always have seen the spot where, she could name, she told me that she could name all the spots where she'd actually, he'd collapsed. So I suppose, you know, if it's that bad then she would have been worse had he died there I think"* (GP1)

This had been mentioned in the patient and carer interview but his wife had not elaborated on it and reflected the question back to the patient.

> *"Patient: It's, it's tougher than you thought it was going to be didn't, isn't it?*
>
> *Wife: Tough on me?*
>
> *Patient: Yes.*
>
> *Wife: I think it's worse on you love (laughs) a lot worse on you love."*
> (Patient 1 with wife)

Patient 1 is an example of joint patient and carer interview where analysis of the interaction between the two showed differences and tensions between their points of view. It is an interview where separate interviews with the patient and the carer may well have revealed additional information (**section 7.5**).

All of the interactions between patients and carers were analysed (no 7, 8, 9, 11, 13, 16)[282] and apart from patient 1 and his wife described above, did not reveal any important additional information. There was a great deal of agreement and encouragement of sharing information between the two. The separate carer interviews (3, 4 and 5) were coded using the framework summarised in **figure 17** and compared with the patient interviews, showing codes were similar. As a result of this analysis the decision was made to present patient and carer themes together as they were so similar.

6.3.2.2 Patient 3: example of patient, carer and HCP interview providing complimentary data

Patient 3 was an elderly gentleman who was seen at home. He had been widowed in the last year, and that was his main concern. He attended day hospice. His son was seen separately at his own house. His GP was also interviewed. The patient interview was long, and he mostly talked about the loss of his wife, as his son said:

> *"You can get him talking. The, the only problem is shutting him up."*

The GP interview described his first visit to her at the surgery:

> *"He was resuscitated even though he'd filled out a DNR form, and brought round, and he was incandescent with rage when he came to see me at the surgery, because they'd resuscitated him and he didn't want to be, even though it was a*

successful resuscitation. And so he's basically had either trouble with his angina or with his heart failure since then, and I think he feels that because he was resuscitated he's been given all this burden of ill health, which he wouldn't have had to deal with had he not been successfully resuscitated."
(GP3)

She goes on to describe that as a result of that he is reluctant to ask for help as he doesn't trust hospitals.

"So that makes life a bit difficult because sometimes when you go, you're more poorly than you think he should be; he sort of waits till the very nth minute of his angina or his heart failure, to ring you up; whereas if he called one a bit earlier, might've been able to do a bit more for him sooner, as it were."
(GP 3)

The patient himself does not mention the successful resuscitation attempt but he does mention many different admissions to hospital and distressing incidents of watching patients die. Like the GP interview he admits he does not ask for help as he is worried about being sent to hospital. This was about a severe angina attack.

"Apparently I'm on almost the maximum dose I can have for, for, for my troubles, so why should I contact doctors? They can't do anything. If I contacted, if I contacted my own doctor and I said I've got chest pains, they'd send an ambulance, they'd, they'd take me to hospital (…) there's nothing they can do for yah. The specialists have told me "There's nothing I can do". There's nothing more they can do"
(Patient 3)

His son does mention the successful resuscitation attempt and they didn't do anything about it at the time as they did not want to make a fuss. He thinks his dad is reluctant to ask for help because it is part of his "old fashioned" outlook on life, that he was brought up to be always independent.

Interestingly the patient thinks that regular reviews by the GP would be helpful, whereas the GP states they do not have time for routine home reviews.

"I'm afraid the days of having time to do that are long gone in general practice. Would be nice to do it for quite a few patients, but it's a time issue rather than a, would I, you know, would I like to issue."
(GP 3)

Day hospice was for the patient a change of scene and company especially since his wife died. His son described the additional benefit of education regarding using his morphine, which he was reluctant to take. His GP describes the benefit of monitoring especially in view of his reluctance to attend the surgery/ seek help.

In this triad all three members were interviewed separately and discussed the same topics: patience reluctance to seek help and benefits of day hospice. The interviews did not contradict each other, but provided additional perspective on the topics.

6.3.2.3 Patient 12: example of patient and HCP interview providing additional information

Patient 12 was a lady in her sixties who was interviewed at a day hospice. The day hospice leader was also interviewed. This patient discussed the support she received from her friend. She also discussed a decision to remain at home rather than move to a nursing home and the adaptations to her house. She was very complimentary about day hospice, but in a general way, referring to friendly staff and trips out.

The HCP interview talked about the time needed to build up a relationship with the patient due to issues in the patient's childhood. They were supporting her with these concerns but it remained difficult and the day hospice leader felt there was much more that could be done, for example she was encouraging her to see a counsellor. She was also not taking some of her heart failure medicine, such as the diuretics, which was leading to more symptoms. Advance care planning had been introduced as part of these wider conversations.

It is understandable that the patient did not discuss these issues with a researcher, and again it illustrates the power of the multi-perspective interview.

The individual triads and dyad cases were interesting and aided a deeper understanding of the data. The key findings, however, were made when comparing the main themes of the thematic analysis between the patient and carer and the HCP groups as a whole. The themes were initially developed separately. However, this resulted in repetition of findings if patient and carer and HCP themes were presented separately and if the data was analysed by shared themes important data was missing. However by analysing across both groups using and looking for

similarities, differences and silences, the important aspect of multi-perspective interviewing[274], five main themes were identified and are shown in **figure 19**. As the Venn diagram illustrates, there were three shared themes: communication and understanding; recognition of palliative phase and decision making and consequences and so similarities and differences between patient and carer and HCP views can be explored. Coping and symptoms was a patient and carer only theme, meaning it was less important to the HCP group, this "silence" is an important finding and is discussed in the next section, **section 6. 4**. Similarly, team roles were not a main theme of the patient and carer group.

6.4 Main patient, carer and health care professional themes

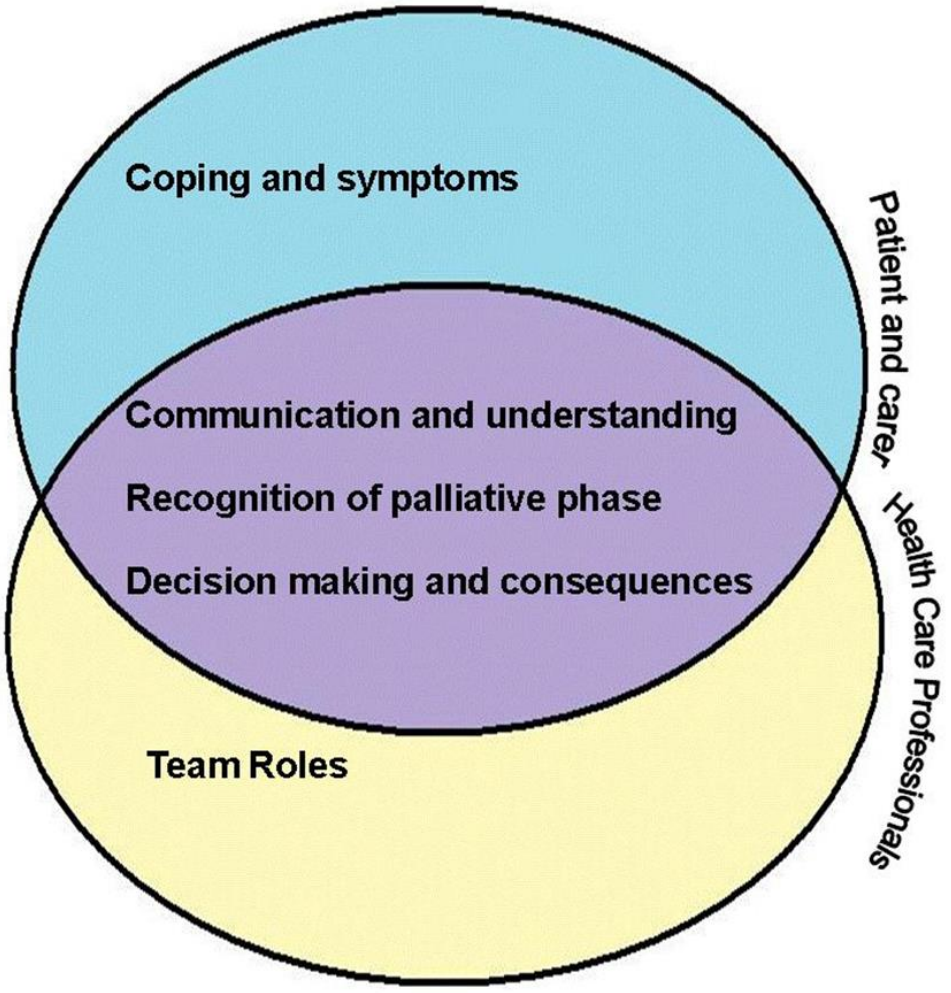

Figure 19. Venn diagram listing five major themes. Coping and symptoms was a patient and carer theme; team roles a health care professional theme and communication and understanding, recognition of palliative phase and decision making and consequences were joint themes

6.4.1 **Coping and symptoms**

6.4.1.1 Coping

"Coping" is a major patient and carer theme and it includes family and community support. There are hundreds of coping strategies and no clear classification system[283]. For this thesis descriptive categories are used; humour, counting blessing, stoicism, family support, social support, life experience and a belief system, see **figures 20, 21 and 22.**

Humour

Wife: And it's so, if, if we talk about things like that, we always joke about them, don't we?

Patient: Make a joke about it…
(Patient 9)

Well I'm going, probably I'll get to that stage and I don't know how I will put up with it, you see. I've never, I've never committed suicide before but (wife laughs) you know, makes you wonder.
(Patient 11)

Well we've been married now for sixty-four years and so no wonder his heart's worn out (laughter) having to put up with me all them years. (laughs) It's had a bit of a strain on it
(Wife of Patient 13)

Counting blessing

Wife: Yes, we're just thankful for every day aren't we NAME OF PATIENT?

Patient: That's right.

Wife: Yes, now the sun's shining and the clocks have changed, NAME OF PATIENT haven't they?

Patient : That's right.
(Patient 8)

I think as well with, we've had four daughters, we've had our ups and downs… but we've faced things together and we discuss things together. I've never felt isolated, and I don't think PATIENT felt isolated as regards any problems, you know, we always feel we could talk things through with us. And we're so fortunate we've got to, to this age that we got our card from the Queen… (laughter) …for our, for our diamond, yes, our anniversary, sixty years, which I didn't expect, which was quite exciting.
(Wife of Patient 13)

Stoicism/ getting on with it/ keeping independent

I suppose the way we cope is the way we've seen previous generations cope, that's, that's the thing. My mother was a, a woman of sayings, one of them being

'there's no such word as can't'. In other words, whatever it was you just got on with it and, but some things, if I had her here I could tell her, there are some things, no, you know, that you just can't do so. But you know what I mean don't you?...and if possible perhaps don't be as independent as I am. (laughter) Do really try and accept help graciously which I find awfully difficult. (laughter) And I'm…I am very, very difficult to help.
(Wife of patient 9)

Q: So has there been ever any times when you've felt overwhelmed by it all?

Patient: Not, not really. I can't, I can't think of anything that's got me down.

Q: No. You just keep, keep going?

Patient: Yeah, just keep plodding on.
(Patient 13)

Oh can't grumble, you know, I'm being well looked after.
(Patient 19)

Figure 20. Illustrative quotes for patient theme coping (humour, counting blessing and stoicism)

Family support-practical and emotional (enduring relationship)

When asked about caring responsibilities:

No, I don't mind it. We've been married sixty-two years and at the altar, for better for worse, for richness and poorness, in sickness in health, till death us do part, and that's what (getting upset) oh I'm sorry.
(Wife of Patient 8)

They live near, and they do meals on wheels on a Sunday, take it turns to bring us a Sunday dinner. (laughs) So that's very nice. And they, I mean DAUGHTER1, as I say, is a nurse. DAUGHTER2 works at my doctor's surgery, so she knows how things work at that end. DAUGHTER3 works for the DSS, so any forms we need or who to contact, she finds out.
(Patient 17)

Q: What, what does your wife do for you?

Everything. Cooking, washing, helps me get dressed. She does really[do too much], she had a bit of a breakdown about a month/six weeks ago.
(Patient 19)

Community / Social support (this is also discussed under symptoms, social isolation)

Whereas at one time you would know the whole street. And I suppose as people have moved on, the ones that we knew who had children at our time, they've all gone, so you lose that bond of neighbourhood friendship, and I think my dad's the same. Very lucky that his next door neighbour, in fact both next door neighbours are quite good. The ones above certainly look after dad very, very well and the

ones below are quite good with him. So yeah, they do have a, a sort of a little neighbourhood group there which provide some sort of support.
(Carer 3)

Cos there's nothing in 'ere now, you know. Used to be nice in here [(housing complex]. Used to be all elderly people but now they're letting them in at fifty-five year old. They don't wanna be playing bingo and sitting. They're just not interested. They go out to work, most of them, you see, so it's...social side of it's going fast. Yeah, supposed to have little trips out and, you know, and go out for meals, but there's none of that now.
(Patient 10)

Figure 21. Illustrative quotes for patient theme coping (family and community support)

Life experiences

It's a, it's a, a, a bonus really that he's got to what he has[age of 78] because and when, when I first met him his mum and dad used to say; He was always told that he wouldn't, wouldn't make it to his teens because he had every illness that they had
(Wife of Patient 7)

I did arrest when I was in hospital last time, you know. All I remember 'em, I sort of come to and I thought what they all fussing about? What are they pulling at me for? You know, there seems to be a lot round me bed doing things at me, and I, I hadn't, I hadn't understood that I'd, you know, arrested (laughs)….But if that's dying, well it doesn't matter . And I know, I was with me husband when he died, and it was just peaceful, you know, he just sort of went to sleep, you know. And that's the way I look at it, you just go to sleep but you don't wake up. I mean when you drop off to sleep, you don't know, do yah, at night-time. You don't know when you go to sleep, go to sleep, do yah? And you don't know for sure whether you're gonna wake up, do yah?
(Patient 10).

Belief systems/ spirituality

I've been a God fearing man an' all, all me life. Let me tell you a little story [about experience in second world war]….I were running to shelter, it were about, I would say a hundred yards up the road,… and what happened was an old man came out and he fell…. Well [NAME OF FRIENDS] were with him and of course they went back to pick him up, but he were a big lad, a big heavy lad, and they couldn't get him up. So they started shouted, and me well I were halfway to the shelter …but your conscience I think it comes to your aid, it. Anyway, I went back, I stopped and went back, I run back of course and helped 'em get him up, and that shelter I were running to had a direct hit….There were twenty-seven killed in it…And that, I just thought me mother had been preaching at me to be good and believe in God and all this all of me life and, and that. Anyway, I said, I thought to meself and I never took any notice of her, you know, but I didn't let her see that. Anyway, I just thought to meself that's got to stay with me has that. Cos when we

settled down afterwards I thought oh God, I could have been blown to bits, you know.
(Patient 11)

Q: Why, why do you think you have no worries about it?

Because I believe in God and I've got plenty of peace, so I don't, I don't need to worry about it.
(Patient 13)

From a patient who described himself as an aging hippy:

Well I'm quite philosophical about it, to be quite honest. I think you're born and you die. So, you know, if my time had come, it had come, and as long as my family were going to be OK, I'd have been quite happy with that, you know. I'm sure there's still a lot to do, but having said that there, no. I've got a fabulous son and a fantastic wife, and they've been my sort of strength really, you know. So, I mean if I went tomorrow, I go tomorrow. Nothing, nothing else I can say about that really.
(Patient 15)

Figure 22. Illustrative quotes for patient theme coping (life experience and belief system)

6.4.1.2 Introduction to theme of symptoms

Symptoms, physical, psychological and social, as well as loss of identity and changing roles of who they were as a person and a couple were very prominent in the patient and carer interviews. It was not prominent in the HCP interviews, even when specifically looking back at the codes for symptoms and quality of life. When it was mentioned by HCPs it was very general using the general term "he was symptomatic" contrasting with the vivid and specific descriptions patients and carers gave.

6.4.1.3 Physical symptoms

As expected, breathlessness and oedema are prominent symptoms. These symptoms are part of the definition of heart failure discussed in **section 1.4**. Breathlessness is also described as "champion symptom" one that is readily volunteered by patients and their families[284] These were fluctuating symptoms but breathlessness in particular was always present to some degree. At its worse breathlessness meant that the patient was confined to bed, or more commonly a chair as they were unable to get into a bed or lie flat.

What I mean, I couldn't lay down at night. I used to spend the nights in the chair most of the time, and that's when I got, obviously, breathless and me ankles and

that were, you know, really swollen and that, because of, I couldn't really go to bed, cos every time I laid down I just felt so sick. It was horrible. I was like that for years and it was awful.
(Patient 4)

The other finding from this quote is the length of time she had the symptoms "years" and this was confirmed by the GP and a separate interview with her daughter. When patient 4 was interviewed she was relatively stable and had in fact improved greatly from the time when she had to sleep in the chair. However, by the time her GP was interviewed after a delay of several weeks, her symptoms were worse. The fluctuating disease trajectory will be discussed further in the theme, recognising the palliative care phase.

Pain was also a prominent symptom. There was cardiac chest pain or more generalised pain due to poor conditioning or co-morbidities such as arthritis. Cardiac chest pain was often not controlled by their cardiac medications or the medication (e.g. Glyceryl trinitrate) was not tolerated leading to significant light headiness/ risk of falls. Some of the patients were on morphine or equivalent medications either for pain, breathlessness or both. This was generally effective although there were concerns expressed by patients about the use of morphine and they generally needed support, education and encouragement from HCPs to use it appropriately. One example of this is discussed by patient 3's carer in **section 6.3.** Patient 11 refused to call his chest pain a pain but "a drag". He spontaneously referred back to this "drag" at multiple times during the interview and it was clearly a major source of distress for him. He described the severity of the drag, as worse than breaking his leg and the chronicity of it made him consider suicide. His wife stated that when asked about pain by HCPs he would deny pain.

Poor mobility was very common and often multifactorial: due to arthritis, oedematous legs, falls or unsteadiness; breathlessness or other symptoms; fear or anxiety and fatigue. It was a significant contributor to the social isolation, discussed below. Muscle ache was also described:

Patient 16: But what, what really hurts are the big muscles in the legs and, strangely enough, this one across here which, which aren't involved other than like swinging your arms. So it's the sort of like the total muscular system is, is feeling inadequately fed with oxygen is how I tell myself.

(Patient 16)

In conjunction with cachexia, muscle weakness and fatigue are due to heart failure being a multi-system disorder[285] and has effects on patients activities of daily living from difficulty in doing house work:

I make bed and then I have to lay down on it, you know (laughter)
(Patient 10)

To being too fatigued to eat:

Yes, he's very tired. I, I puree his food now, because I would give him his lunch and he would take about three hours to eat his lunch and he was exhausted after it. But now I give him the pureed food and he's much better.
(Wife of patient 8)

Other symptoms such as nausea and itch were less common but overwhelming for the individuals affected. One patient described the effects of itch on both him and his wife:

All you need is a good nurse[wife] (laughter) that comes running any time you shout, whatever time of the night it's been. (laughs) There's been some horrendous nights haven't there?...

She's put up with things that a normal wife probably wouldn't put up with, you know, like getting her up early and going…into the shower and then back into bed and couple of hours later I'd have to go back in the shower again, you know, and being so ill herself, which she was…I don't know how she did it.
(Patient 7)

6.4.1.4 Psychosocial and changing role

The above quote also demonstrates the effects are not just on the patient but on the carer too. This overlaps with the coping theme: family support-practical and emotional (enduring relationship). Carer strain was identified and there was a change in the patient wife relationship from "normal wife" to "nurse".

Psychological issues such as poor concentration and low mood were also identified. In addition patients struggled with their change in role to a patient and loss of self-identify (personhood). There were many descriptions of being fit and sporting and other achievements prior to being ill:

M: I used to do a lot of swimming, you see, and being used to it…

F: He's always been a fit man.

M: Well I were a gymnast for quite a long time.

F: Yes, played football and, you name it, he's done it.

M: Did a bit of boxing, didn't I?

F: Yes, he has, yeah.

M: Quite a lad in them days.

F: Yes, he was quite fit when he was young.

M: And, physically I don't think I could be hurt, but by gum this illness has caught me out. Ooh.
(Patient 11)

Social isolation was a very distressing symptom for many patients, and for some it was by far the worst symptom. It was a symptom that appeared to become more severe over time. For example, it started with being medically unfit to drive (a milestone recalled by many patients) to being house or even chair or bed bound.

Patient 10 describes being "caged in." Her HFNS 3 had recognised she was becoming depressed and referred her to day hospice. Like for many of the patients at day hospice it was only trip out of the house and was very much looked forward to:

That's me day out, I class that as me day out. Wednesday's tomorrow (laughs). And I always have a nice dinner, you know. I always pick something that I wouldn't have at 'ome, you know.
(Patient 10)

HFNS 3 commented her mood was improving and she thought it would be likely the patient would be discharged from day hospice soon. This reflected an integrated model of care, with referral to specialist services for a specific symptom and discharge when it had improved.

Other reasons for social isolation were being unable to interact with friends due to illness, because they or the friends did not know how to act. This would also relate to loss of personhood described above. Day hospice was helpful for providing peer support.

6.4.2 **Communication and understanding**

Communication was an important theme for both patients and carers and health care professionals. However, there were considerable differences between patient and carers and health care professional with regard to communication. Communication and understanding were often linked.

The first finding is the readiness of patients and carers to talk about death and dying. Reflexivity will be discussed further in **chapter seven**, but it very important with regard to analysis of the communication theme. It was a clear finding that patients and carers in this study readily and openly understood and discussed their limited life expectancy, death and dying. Analysis of the timing of when these topics were introduced by patients and carers, demonstrated it was often at the start of the interview, with the open question of what do you understand by your condition.

> *Q: So the first question is what do you understand about your dad's condition, about his heart condition?*
>
> *Carer 3: I know it's terminal and very little can be done to relieve the problems that he's got. I suppose that's the nub of the matter.*
> (Carer 3)

How patients and carers gained understanding that their condition was life limiting was variable. Some were told by HCP, others worked it out themselves. More unusual was a patient's wife who worked it out from the discharge letter:

> *As, as months went by, we was in the hospital again and this time it was printed out, it was severe left ventricular failure [previously left ventricular failure].*
> (Wife of patient 8)

Patient 16 came to a gradual understanding that his condition was "permanent" from watching the education videos that were supplied with his telehealth monitoring system. He described it was implied during a long stay in hospital but never openly acknowledged.

> *It slowly dawned on me one day, when I was watching one of these tapes on the thing, and I, I thought oh goodness me, that's me, I'll be like this forever.*
> (Patient 16)

Communication between clinician and patient is particularly important.

It is important to reflect on those patients where the communication between patient and clinician did not go so well. These are cases that are different to the others (deviant case analysis), which can often reveal interesting additional findings[271].

Patient 14 is a notable example. She asked about her prognosis, was told unexpectedly that she had a prognosis of months. Even despite this she was very clear that it is the responsibility of the doctor to tell the patient the truth. Her concern was the way she was told not that she was told.

Patient 7 also had a poor communication experience:

> *And I'd been for something I can't remember what it was and he just come right close and he said "You know you're in heart failure don't yah?" Well I was so shocked, I said "Well will I make it out of surgery?" He says "Well possibly". And from then on it started to, I had, I said "Well I'm not going to him again, he's arrogant". So I went to another doctor, Dr GP, and he was far more sympathetic and a right good laugh. We could have a, we spent more time laughing than (Q laughs)…*
> (Patient 7)

This patient was very accepting of his poor prognosis and demonstrated many different coping styles. He was able to discuss his future care with the HFNS, which was important as he was very keen to avoid hospital admission. He preferred HCPs who mirrored his coping strategy of humour.

These "deviant cases" illustrate that even when the conversations were difficult it was still important to patients that they took place.

Other patients found conversations about change in focus or care straightforward and many even positive, or welcomed them. As shown by **figure 23** some patients initiated conversations about change in the focus of care.

Patient 13 described a conversation with his GP about DNAR:

> *Patient 13: We were discussing, and we'd thought about it before.*
>
> *Q: Yeah. And how did it go with Dr GP, the conversation with Dr GP?*
>
> *M: Easy*
> (Patient 13)

Patient 2 again about DNAR discussion:

> *Patient 2: Well I was told that if I had another cardiac arrest then the heart would be damaged beyond repair, and me quality of life would be not very good, so I decided myself to sign the do not resuscitate form. Then the doctor agreed with me, the doctor says "I think you've made the right decision" so. I think you can basically say it were a joint decision between me and the doctor.*
>
> *Q: That's, yeah.*
>
> *Patient 2: Yeah, and these are aware of it here, the do not resuscitate, so. I mean everything's in place really, I feel content knowing that there's nothing they can do, yeah, I don't bear any malice to anybody.*
> (Patient 2)

Interestingly the HCP (GP2) reflection on the conversation was that it was a very unusual situation for him. He was an experienced GP but found that conversation so unusual he wrote a blog post about it.

Another GP,

> *But I didn't discuss prognosis with him as such. I mean he knew that he had a terminal condition and I couldn't, I, I would, I'm not the type, you know, I, I, I'm not, I've never been totally confident about saying, you've got X time to live, and certainly wouldn't do it in heart failure, because I don't know what the terminal event would be. But he knew that, that he was, you know, his life was limited, but I didn't discuss it with him though, no.*
> (GP 1)

This GP had only discussed DNAR twice in his career.

HFNS 2 expressed her worries about end of life care conversations

> *Ah. I, I think that just depends on them and, and how you are on the day or the week or the month and the year as well, and I think that's why it is, that, that's why we find it still really challenging, and I think everybody does because sometimes it goes really well and other times it just goes really badly, and you just come away thinking oh God, you know, I didn't handle that very well, or oh my goodness, you know, that went down the wrong track, and it's the bad experiences I think that make you quite wary the next time to start a conversation.*

These HCPs were selected by patients and were generally supportive of palliative care, and still these HCPs were not often having conversations about change in focus of care with patients.

The HCP (SPCP1) nominated by patient 12, discussed as an example case in **section 6.3.2**, illustrated an important aspect of communication, which was building up a relationship, and that often repeated conversations were needed.

6.4.3 **Recognition of palliative phase**

Both patients and carers and HCPs discussed the fluctuating disease trajectory of heart failure. There were quite dramatic changes with worsening function and symptoms; with periods of stability and even improvement.

Linked to the previous theme of communication a major concern of HCPs was timing about conversations and change of focus of care. This is illustrated by this quote from a HFNS.

> *Although he does recognise the fact that he's getting towards the end of his life and he, he actually asserts this himself, so it's not, it's not a mystery, although we haven't actually had the discussion as to, because he's not ill enough at the moment, to warrant discussions about end of life care, where he wants to have it and certainly, in terms of DS1500, he's quite a long way away from that.*
> (HFNS 2)

So despite the patient himself recognising that he is getting towards the end of the life, the HFNS is still thinking that it is not time. The clinicians were clear that palliative meant irreversibly deteriorating the periods of stability or even slight improvement meant that the patient could not be palliative. This led to the situation described in the quote above, when conversations and a clear change in focus of care were delayed because a patient was not irreversibly deteriorating.

Another example of clinician concern about timing of conversations and change in focus was from a HFNS talking about a time when she got the timing wrong:

> *HFNS 3:For the vast majority of heart failure patients it's really hard to predict and get it right sometimes. So, you know, because once we're, once, once we're happy or confident that, you know, they've hit the palliative phase we can then step in and do all the stuff. It's the grey area where you're not sure, and sometimes you hesitate and shouldn't have, and other times you bowl in and you've bowled in too quickly, so.*

Q: So what happens if you bowl in too quickly, what's the problem?

HFNS 3: Well there was a guy that, oh probably about, it was just before Christmas and I'll never forget it because I did bowl in too quickly, and he, he'd had a significant deterioration, he'd absolutely given up himself, the family were in a complete state of panic, and I just thought to myself, crikey, he might well die over the weekend cos he's just given up. So went in there with the, you know those last few days of life booklets?

Q: Mm hmm.

HFNS 3: Well I've forgot, forgotten what the thing is, gave that to his wife and caused absolute pandemonium in the family. They, they then were sitting there as a vigil to this man and he's still alive (laughs) six months later, and the GP was horrified when he went in that they were holding this vigil for this man who was going to die, and when he decided that he wasn't going to give up and he sprung back to life, he, he became quite well. So yeah, I think I bowled in very quickly there because I think it was just a pressure pot in the house as well. I thought oh my God, he might just die this weekend, so.
(HFNS 3)

However, the continuation of the story is that the patient and their family were understanding of the situation and joked about it with her.

Interestingly, because of the sampling strategy many of the patients interviewed had been palliative for a period of months or even years. When I asked HCPs about this they reflected back that it really was not a concern. There were a few comments about concern about limited capacity of services but overall once the decision had been made to take a palliative care approach, there was no longer any difficulty. All of the concern (from HCPs) was before the decision was made.

Only a few SPCP were interviewed but interestingly this day hospice leader expressed that they were concerned about heart failure patients coming too late, rather than the concern about referrals that were too early

Does it, does it make a difference to you thinking about prognosis, does it make a difference in how you care for PATIENT NAME?

A: Well it, it does actually make a difference to what we do in day hospice because it, it, with, with PATIENT NAME not so much because it's, she, I don't think anything would really change. However, if we get a patient referred to day hospice who was clearly much worse, well you'd have to get in there a lot quicker with a lot of the decision making process, and this happens a little bit too often, is that we

often get patients referred too late, PATIENT NAME hasn't been. It's, it's ideal, it's a timely referral in a way that allows us to get to know her, allows us to help her make difficult decisions rather than it being a knee, knee-jerk reaction of getting the services and getting things sorted out quickly. And that's when patients lose control, when they are too poorly and it's a knee-jerk reaction, rather than it being a thought out considered process, which we try to achieve, ideally.
(SPCP 1)

Patients were more accepting of uncertainty and positive about it at times as they felt it gave them extra time with family or a period with fewer symptoms

Patient interviewed in the hospice where he had been admitted for terminal care:

Patient: Yeah, I think I've been very, very fortunate, I've been very fortunate and I'll not keep harping back to it. But, you know, from, from a bad prognosis, to live five years to see a grandchild is something special, really special.

Wife: That's kept you going we think.
(Patient 1)

6.4.4 Decision making and consequences

6.4.4.1 Decision making

Figure 23 summarises the decision making for each patient. It demonstrates a variety different decisions emphasising that this is a complex area. Note that patient initiated decisions did occur.

Patient 1) Referral to in patient hospice for symptom control/ terminal care by HFNS as difficult symptoms, but aware of life limiting illness previously
Patient 2) Day hospice intermittently for several years, initial decision making about palliative care (especially resuscitation) made by patient when decision making about transplant and his lack of suitability
Patient 3) Patient independently decided not for resuscitation in 2005 (when relatively well) and discussed with GP who signed DNAR form but was resuscitated in hospital and furious about this. Palliative care approach since successful resuscitation
Patient 4) Difficult symptoms especially nausea, GP initiated and concurrent social isolation post bereavement so day hospice via HFNS
Patient 5) HCPs noted deterioration, patient focussed on not going back to hospital because of bad experience
Patient 6) Gradual deterioration in functional status over two to three years recognised by patient and HFNS and day hospice very recently
Patient 7) Deterioration in symptoms over last year or so and patient recognised himself not going to get better
Patient 8) Deterioration in symptoms over last 18 months but not coherent palliative care approach discussed with patient until HFNS involved
Patient 9) Valve surgery seven years ago, not as successful as hoped and multiple medical problems since, but palliative care approach because of cancer
Patient 10) Referred to day hospice because of low mood and social isolation rather than prognosis or poor performance status, open and philosophical about life limiting illness and will discuss openly/ initiate conversations
Patient 11) Diagnosed with HF due to amyloid and cardiologist therefore identified as palliative due to poor prognosis with this diagnosis and also HFNS noticing progressive symptoms
Patient 12) HFNS to day hospice, not clear why as did not interview HFNS and patient not clear but day hospice leader felt appropriate and left time for getting to know patient as completing two separate eight week blocks at day hospice.
Patient 13) Strong decision making from patient and family especially triggered by difficult hospital admission, but had thought about early in diagnosis and had explored "living will"
Patient 14) GP told her about poor prognosis because she asked if she was getting better, unexpected answer.
Patient 15) Discharged home to die in next few weeks 3 years ago as unable to have valve operation.
Patient 16) Patient worked it out for themselves that not going to get better from pieces together various bits of information including telehealth
Patient 17) Being investigated for heart failure and then diagnosed with myeloma. Palliative care approach due to cancer but heart failure causing most of current symptoms
Patient 18) Referred to day hospice in 2005 by cardiology consultant (reasons unclear as a while ago) but remained under day hospice once a month as difficult symptoms and especially comorbidities and multiple drug reactions that felt too complex to discharge
Patient 19) On GSF and followed up therefore by district nurse. Also sees HFNS. Not clear why on GSF but note has cancer of liver which could be reason

Figure 23. Decision making for palliative approach to care/ transition to palliative care approach

Information from patient (and carer if available) interview and HCP interview apart from patient 14. As a result of sampling strategy likely to capture patients with longer palliative care trajectory

Once the decision had been made the consequences seemed to flow naturally from that. There did not seem to be any dissent in the team or problems with accessing services if that was required.

The only exception was being put on a palliative care register, where cancer patients were more automatic, heart failure patients were not:

Q: OK. And so you mentioned the, the gold standard framework that you tend not to use that with heart failure patients?

GP 3: We do if necessary, if we feel there's someone that should be on the gold standards framework, who is terminal in the sense it really is the last phase of their life, then they do go on and we do involve the heart failure nurses in our, they may not be free to come but they are invited to the meetings so that we can discuss relevant patients with them.

Q: And so, and when you say really terminal, what, what's your sort of (...) just like, you mean like last few months, is that...?

GP 3: Yes.

Q: Yeah, yeah.

GP 3:Yes, cos otherwise the list of people that we have that are not actually dying is colossal and you can't talk about them all in a gold standards framework meeting, you'd never get any useful sort of management plans for the ones; we tend to discuss the ones who are really needy and the ones who don't have a particular need at the moment we don't talk about, and that, sometimes that means they're very poorly and close to dying but the care's completely sorted so there's nothing to talk about, or it may be that we're trying to avert a crisis with some people who are more able, not as ill, because we don't want them to deteriorate unnecessarily. So it's, it's on, on an, an as-needed basis, according to the patient's health at the time, if that makes sense.

Q: Yeah, no, it does. And so would you, would you say it's more cancer patients or more heart failure patients or...?

A: More cancer patients. As I say, the heart failure ones are included when we feel it's necessary, but it's usually in the very end phase of their illness.
(GP 3)

6.4.4.2 The consequences of palliative care approach

The consequences of a palliative care approach were numerous and individual.

Many patients accessed day hospice and as discussed in symptoms and coping it was helpful for social isolation and peer support, things that patients had talked about as problems or reducing their coping mechanisms. Some received support with symptoms such as oramorph for pain or breathlessness.

They were able to be supported to remain at home, with equipment, carers and additional support such as access to a hospice helpline. They were able to make decisions about future care planning such as preferred place of care and DNAR decisions.

These decisions were important to patients as many expressed rather than wishing to die at home had a wish to stay out of hospitals because of terrible experiences in them.

> *The noise started in the hospital at half past six on a morning, early morning shift of nurses coming in and doing those who had messed the beds, you know. But it was the noise that they made doing it and the lights are all on, and that was still happening at half past eleven at night. I said "When do I get any sleep?" So eventually I grabbed the doctor and said "I must go out. If I'm going to die I'll die in bed at home, not here". It's too noisy, wouldn't be able to die for people making a noise.*
> (Patient 7)

Very importantly patients were able to put their affairs in order such as plan funerals and have significant conversations with family members. Often after that they put it out of their mind or just refer to it in light hearted way:

> *Patient: Oh well I'm plan, planning ahead for the future because I know what's going to happen and I want to be prepared for it. I don't want to leave WIFE with a, a lot of odds and ends to tie up. They'll all be ready and in place.*
>
> *Wife: He still hasn't got, shown me how to do the television yet (laughs) so he can't go yet.*
>
> *Patient: Well SON will show you how to do that.*
> (Patient 13)

The above quote is an excellent example that planning ahead is important to patients and their families and much broader than simply planning where they wished to be cared for at the end of life.

Some unmet needs remained. A reoccurring theme was lack of paid carers, which was a real concern, especially for patients living on their own. There were some unmet needs with regard to deep conversation, which will be discussed in **section 7.4**. One patient felt the day hospice nurses "petted him" too much and felt distressed by seeing a young cancer patient with significant weight loss. Overall, he still enjoyed day hospice and continued to attend.

6.4.4.3 Comparison with cancer

HCPs and some patients made comparisons between heart failure and cancer. The wife of patient 1 felt that the mode of her husband's deterioration was worse than anything in the cancer line. Other patients queried hospice referrals if the patient did not have cancer.

HCPs mentioned cancer more frequently and compared the disease trajectories of cancer and heart failure. They perceived that it was much easier to tell when a cancer patient was palliative as they were irreversibly deteriorating.

6.4.5 **Team roles**

This was a major theme of HCPs but considered less important by patients and carers .

Teams were very fluid, with different roles by individual members of that team in each patient. They may never meet but seemed to respect each other's input. Communication was often on as needed basis, such as leaving task messages on the computer.

Relationships between individual team members were described in very positive terms and with some pride in the good relationships they had with other teams. This was mainly between GPs, HFNS and day hospice staff although team members such as cardiologist and district nurses were also mentioned. Negative comments about relationships with other team members were rarely discussed.

One example, of a less developed team relationship was described by a specialist palliative care professional, as part of a reflective comment suggesting possible barriers of time and the specialist palliative care team being too exclusive about their role.

> *A; The only thing that kind of like I think which is a real shame is, is, is that we don't work particularly very closely with the heart failure nurses, and that's probably our fault, rather than theirs, cos they're very busy. But I would like, in some way, to try and improve that because we've got a, you know, and maybe kind of learn from each other from that.*
>
> *Q: Have any ideas or...?*
>
> *A: How to do that?*
>
> *Q: Yeah.*
>
> *A: I, I, I think maybe, as a team, we need to be a little less precious about things, and, and, and be a little bit more inviting in really. I, and I, and I think it's very hard for the heart failure nurses because they're, they've got such a huge workload with very little capacity to be able to share workload and the, you know, it's a, it's a shame cos it would be nice in some ways, for, if they were struggling with some end of life stuff, maybe be appropriate to hand it over. That could be something we could maybe do to help, kind of help each other as well.*
> (SPCP 2)

There were different approaches between different specialties and disciplines.

In terms of timing there were two approaches to care: regular visits such as by the HFNS and reactive care, as offered by most GPs. GPs would not review regularly, but encourage the patient to visit when needed. Patient seemed to appreciate the regular review (see case study patient 3). Another difference was between a disease specific approach (notably HFNS) and generalists. Heart failure specific management was often complex and required careful balancing of treatments and potential side effects, and monitoring of bloods and vital signs such as blood pressure and regular review. Co-morbidity was common, where generalists were more adapt at management than the HFNS.

Re-analysing patient transcripts in light of these findings demonstrated that patients viewed HFNS as specialists with their main role as monitoring and adjusting tablets. GPs also recognised that patients did not see them as specialists in heart failure and

as a result may be reluctant to change the focus of the patients care out of concern that specialists, in particular, cardiologists, may not agree and the patient would be more likely to respect the specialist opinion. Patients' view of GPs was that they were very busy and as a result did not want to disturb them unless it was absolutely necessary.

6.5 Discussion

6.5.1 Introduction

This chapter explored the perceptions of patients with advanced heart failure, their carers and HCPs regarding the transition to a palliative approach to care; and the effect on their subsequent experience of advanced heart failure. For the purpose of the thematic analysis patient and carers were one group and HCPs were another group. Five main themes were identified, with common themes in which difference between the groups could be explored and groups where themes were only emerged in one group (i.e. the other group were silent) were identified.

6.5.2 Coping and symptoms

As illustrated by **figure 20, 21 and 22** coping was an important theme for patients and carers. Coping has been defined as the process of managing external or internal demands that are perceived as taxing or exceeding a person's resources. It generally refers to conscious effort, excluding strategies such as defence mechanisms which are beyond conscious thought. Coping tends to refer to adaptive or constructive coping strategies but maladaptive coping can and does occur "non-coping"[283, 286]. Coping is not just an individual response but strongly affected by social support, which has a significant research literature documenting the psychological and physical benefits of social support[286].

They were mostly constructive coping mechanisms. Community and social support was maladaptive in many cases because of changing social circumstances that meant patients were more socially isolated. These circumstances ranged from losing a driving licence due to illness to becoming housebound. There were other factors such as communities being less tight knit or patients moving into retirement and also bereavement. Some of the constructive coping strategies such as being independent had the potential to become maladaptive if it prevented the patient or carer from accepting help. Additionally family support was an important coping strategy, but carer strain was a significant problem. It is interesting to compare the coping strategies identified with the literature regarding hope in the terminally ill. Humour, meaningful relationships, not being isolated, being valued as an individual (comparable with personhood in this analysis), spiritual beliefs and the

determination to succeed (comparable with stoicism in this analysis) are all important[125].

The important message for clinicians is that patients with a palliative approach to their care do "cope". Clinicians may be concerned about taking away hope by having conversations about palliative care[23, 68, 81].

There was a wide variety of distressing symptoms often reflecting a poor quality of life for patients and their carers[287, 288]. Social isolation, which also related to coping was particularly distressing. It is a significant finding that symptoms were not a prominent HCP theme. There could be various reasons for this such as HCP factors, perhaps focusing on prognosis / when the right time or on issues such as monitoring medication, blood pressure and blood tests. There were also patient factors. There was the tendency to underplay what were very distressing symptoms: expressing feelings such as there is nothing they can do about it. A commonly expressed reason was that they would just send them to hospital, often without assessment. Patients were keen to avoid hospital. It meant that patients would wait until symptoms very severe until they (or a carer) would seek help. This is discussed in the case study patient 3. Additionally, some patients felt that symptoms were not the concern of a professional He "he's more the heart man" (patient 7) or were reluctant to contact the GP because they were concerned they were too busy.

This is very important for recognition of palliative care based on needs assessment; patients are not volunteering symptoms and or HCPs not registering them and so need to specifically and proactively assess symptoms and not just obvious symptoms such as breathlessness but other physical symptoms and psychosocial and spiritual concerns (loss of identify and changing roles) and carer concerns.

Patient factors are essential to consider and not recognised sufficiently in current policy, should be at the centre of **recognition** and delivery of services/care. A patient centred approach would focus on reducing symptoms and preventing unnecessary hospital admissions and reducing social isolation.

6.5.3 **Communication and understanding**

The contrast between patients and health care professionals with regard to communication is stark. Patients recognised the importance of conversations about the change of the focus in their care, even if they found the conversation difficult. Some patients even initiated conversations about their poor prognosis. However, the contrast with the clinicians suggest that it is clinician factors more than patient factors that are preventing more widespread conversations about end of life care in heart failure. Unlike in Barclay's systematic review[23], conversations about end of life care did happen in this group, but perhaps is not unsurprising as they were purposively sampled to be patients with a palliative approach to their care. However, it remains an important finding that conversations about end of life care, in heart failure can and do happen, and as discussed in **section 1.5**, there was an impression that this is due to or as a result of the palliative care approach. It is interesting to reflect about the clinicians described by patient 7 and 14, who did discuss prognosis with patients. The patients' perceptions were that the manner of the conversations which was not satisfactory and they did not return to those clinicians again. This may led the clinicians to think that it was the content of the conversations i.e. discussing prognosis which was the problem, when this was not the case. This may lead them to be cautious about discussing prognosis again.

6.5.4 **Recognition of palliative phase**

As expected from the literature on disease trajectories, all groups described a fluctuating disease course, with periods of stability and even improvement during a palliative phase (**see figure 2**). Patients accepted this uncertainty and at times found it helpful, in that they perceived that had longer period of time with loved ones than expected. HCPs worried about the fluctuating disease course and found it difficult to accept a palliative care approach when patients were stable or even improving. The decision to implement a palliative care approach was preceded by prevarication on the part of HCPs

This is a key part of the mixed methods and will therefore be discussed in detail in **chapter eight** under "transition to a palliative care phase".

6.5.5 **Decision making and consequences**

The important aspect of decision making for a palliative care approach in this population of patients was that it was due to a variety of reasons not to do with

prognosis or HCP recognition of the last year of life. In some cases it was initiated by patients.

The consequences naturally flowed once the decision was made and demonstrated that the key issue is recognition and communication of the palliative care approach rather than implementation. The consequences were mainly positive both for patients and carers although some unmet needs were identified. In despite of their concerns prior to the change to a palliative care approach HCPs were very satisfied with this care, even if the patient did then improve.

A more detailed discussion of GSF / palliative care registers is included in **chapter eight** as part of a discussion of the mixed methods.

6.5.6 Team roles

There was a great deal of fluidity of roles between the teams and indeed there were some duplication of tasks, for example, bloods were taken twice or an advance care plan form was duplicated unnecessarily. The lack of clarity regarding team roles has another potential disadvantage as no one professional was taking responsibility for a task then there was potential for them not to happen. This is particularly important, with regard to initiating potentially difficult conversations.

The different team roles could make it difficult for patients who wished to initiate conversations about a change in their care. They might perceive that the HFNS role is just with regard to monitoring and heart failure medication. However, more positively, the regular reviews would mean they could build up a relationship with the HFNS. Patients felt that GPs were busy, patients also needed to contact them as they did not offer routine reviews and they would be seen less frequently by their GP if HFNS were involved. All of which could act as barriers to GP and patient conversations about a change to a palliative care approach.

6.6 Summary

The multi-perspective approach to recruitment was successful. Analysis of patient and carers as one group and HCPs separately as another group allowed major themes to be identified and then multi-perspective analysis enabled comparison between these two groups. In particular, common themes in which difference between the groups could be explored and silences where themes were only

emerged in one group were identified. Coping and symptoms were clearly important to patients and carers. The relative "silence" from the HCP group was an important finding and highlighted the minimal emphasis on symptoms by the HCPs. This may indicate that systematic on-going symptom assessment as part of proactive care is not reliably implemented by HCPs, even in this selected population where some of the HCPs were specialist palliative care, this silence is notable. Coping was important to patients and carers, and HCP need to identify that patients can and do "cope" and recognise times when coping was reduced for example, social isolation and consider introducing services such as day hospice that restore that balance.

Patients and carers readily and openly discussed that their disease was life limiting. This contrasted with HCPs concerns about taking away hope. As expected from the literature on disease trajectories, all groups described a fluctuating disease course, with periods of stability and even improvement during a palliative phase. Patients accepted this uncertainty and at times found it helpful, in that they perceived that had longer period of time with loved ones than expected. HCPs worried about the fluctuating disease course and found it difficult to accept a palliative care approach when patients were stable or even improving. The decision to implement a palliative care approach was preceded by prevarication on the part of HCPs and was often initiated by patients and their family. Once the decision was made the HCPs anxieties were unfounded and the consequences which flowed from the decision were generally very beneficial for patient and family, although some unmet needs remained.

HCPs were very concerned about team roles. The reactive nature of primary care inhibited initiation of a palliative care approach. The fluidity of team roles also meant that responsibility for decision making and communication was not clear, each member of the team leaving it to another member of the team to make the decision about a palliative care approach.

This group of patients were clear that they wished to discuss their limited prognosis and a palliative approach to care with HCPs even though these conversations were potentially difficult. HCPs were concerned that it was not the right time, that they were not the right person or that they would take away patient hope if they initiated these conversations. However once the decisions about palliative care

approach was made and implemented it led to benefits for patients and their families and HCP fears about taking away hope were not realised.

7 Strengths, limitations and methodological issues arising from the qualitative study

7.1 Introduction

In this chapter, methodological issues relating to the qualitative part of the thesis will be discussed. The approach to critical appraisal will be explained before discussing the strengths and limitations of the study with particular reference to reflexivity. Joint interviewing of patient and carer participant as opposed to individual interviews will be explored. A difficult issue that arose as a result of the ethics submission with regard to how to describe a palliative care patient in the participant information sheet will be explored in detail. The chapter will conclude with a section on recruitment as this is a recognised area of difficulty in palliative research. Academic writing by convention avoids the first and second person pronoun as it is less objective. This chapter is by nature reflective so the first person narrative voice will be used unlike in other parts of the thesis.

7.2 Critical appraisal of qualitative studies

As with all research, there are poorly conducted and reported qualitative studies[267] and it is important to reflect on the strengths and limitations of the study.

> *"All research is selective; there is no way that the researcher can in any sense capture the literal truth of events"*[289]

There are considerable debates as to the use or nature of quality criteria that may be used to appraise qualitative research[290]. These debates are centred on different viewpoints regarding the nature of knowledge. One extreme viewpoint may be that social reality does not exist outside of human constructs or accounts, therefore assessment is impossible and irrelevant[291]. This viewpoint is not consistent with academic debate and will not be used here. The other extreme may be seen as that there is a single irrevocable reality or truth which is entirely independent of the researcher and the research process, again difficult to reconcile with qualitative research. All research, including quantitative research is selective and hence subjective[289]. The theoretical framework regarding the nature of knowledge used in this thesis is constructionism and has been discussed in **chapter five**. Also to be considered when critiquing qualitative research is whether an external checklist or external list of criteria should be used. There are numerous examples of such

checklists[133, 271, 277, 289, 290, 292, 293]. The uncritical use of a checklist without any theoretical understanding would result in a narrow evaluation of credibility, for example from a positive perspective. The use of checklists may have resulted in authors adding information to papers; to make sure they fit the checklist; "the tail wagging the dog"[294]. Therefore specific checklists will not be used in this thesis. Finally, it is important not to be overcritical as there is a difficult balance between theory and practice; feasibility and desirability; "all research is selective, there is no way that the researcher can in any sense capture the literal truth of events"[289].

7.3 Strengths and limitations

7.3.1 Main strengths of this study

The qualitative study asked a clinically important question regarding the perceptions of patients with advanced heart failure, regarding the transition to a palliative approach to care and the potential consequences. The question is potentially relevant to a large population of advanced heart failure patients with unmet palliative care needs. This question has not been explored before in previous research and arose from a gap in the literature. It is an area of interest and priority in current health care policy.

This is the first qualitative study in the literature, as far as I am aware, that has focussed on the experience of patients with advanced heart failure (and their families and nominated HCPs) where it has been recognised that a palliative care approach is appropriate. This involved purposive sampling of a potentially difficult to recruit group, those with heart failure, who are actually experiencing a palliative care approach to their management. As demonstrated by the GPRD study (**chapter four**) this is a small percentage of patients with heart failure. The strength of this is that it allowed further exploration of the transition to a palliative care approach and the effects of that change.

The multi-perspective interviews (patients, carers, and HCPs) is also a strength and it is particularly useful for providing practical recommendations about services[274]. This meant that the study has been able to go beyond descriptions of barriers and unmet need to propose specific ways in which a palliative care approach could be implemented for patients with heart failure and the effects of that approach to care.

This will be explored further in **chapter eight**, when all of the separate studies in the thesis are integrated.

The method used allowed for rich descriptions of the real life experiences of patients, their carer and health care professionals. Nineteen out of thirty (63%) of potentially eligible patient participants took part in the study, which for a palliative care study is a good recruitment rate[295] and the patients, although purposively sampled, represented current patients with advanced heart failure having a palliative approach to their care. Furthermore, the ages of patients, represented the population with advanced heart failure, with most being older. There was a good range of HCPs interviewed including GPs, HFNS and Specialists in palliative care but no cardiologists were interviewed as they were not nominated by patients.

The analysis was explained in a transparent way. The topic guides and coding frameworks were presented. I particularly looked at negative or deviant cases where my explanatory scheme appeared weak or was contradicted by the evidence[295]. This was particularly useful technique when I was deciding the final themes and the fact that the same themes were not present in patient and HCP interviews, which was a very important finding. Additionally, it was useful for specifically looking at the possible negative consequences of a palliative care approach. Various 'quality control measures' have been suggested that may add rigour to qualitative analysis but, as discussed above with regard to checklists, their use is debated[289]. Multiple coding was used, with more than one researcher independently coding the data. In practice it may be difficult for researchers to be independently assigning the same meaning to data[271], and it was used more to encouraging thoroughness in interrogating the data and alerting to possible alternative interpretations[289]. Triangulation described as more than one method of data collection (quantitative or qualitative) to answer the research question and has been suggested may improve credibility of analysis. However, it may be more useful if seen as complementary rather than competing perspectives, and the term 'crystallisation' has been suggested as an alternative term to 'triangulation'[289]. This will be discussed further in **chapter eight.**

7.3.2 **Main limitations of this study**

The setting and participants should be considered. The majority of patients (nine out of 19) were recruited from Scarborough, the centre with the integrated palliative care and heart failure service. This is a potential limitation as there are few such services in the UK and so it could be argued this is a less representative sample of the UK as a whole. There were patients recruited from Hull, York and Harrogate who do not have integrated palliative care services for patients with heart failure. Furthermore, the study was not aiming to be representative but specifically select patients where a palliative approach to their care had been taken and so had conversation(s) with their HCPs about this approach. This meant that potentially, lessons could be learnt from the patients and the HCPs who had access to the integrated service. In addition, having a variety of recruiting teams (HFNS, GPs and specialist palliative care broadened the experiences of care of the patients recruited.

Similarly seven out of 14 of the HCPs were the same HCPs that recruited the patient for the study and many of the HCPs were interested in palliative care for patients with advanced heart failure. It could be argued that these were a "keen" group of HCPs and not representative of HCPs in general. However, the purpose of the study was to gain insights from HCPs where the change to a palliative care approach had taken place and these are more likely to be HCPs who are interested in the area and not meant to be representative of the population as a whole.

Other limitations include being unable to recruit equal number of men and women and the lack of ethnic minority patient and carer participants. The ethnicity of the participants represented the population in the areas and those that would access palliative care services in this area. However, palliative care researchers have been criticised for failing to engage with minority groups[290] and it is a limitation that ethnic minorities were not represented. The patients that were recruited, as a result of the way they were sampled were patients who had a longer period of palliative care; those that deteriorated quickly after a palliative care approach was introduced were less likely to be able to take part in the research. However, the group with a longer palliative care phase were an interesting group as I was specifically able to probe the consequences of this both with the patients and their carer and the HCPs.

Another limitation was the lack of non-family carers; two non-family member carers were identified but one declined to take part and the other did not return their form. In addition, there were only three individual (as opposed to joint) carer interviews. It was not the main focus of the study but carers are a very important group and potentially neglected in palliative care research[291, 292].

The aim of the qualitative study was to explore perceptions of patients where a palliative approach to their care had been taken. This could be anywhere along the disease trajectory from diagnosis to close to death, however, with the exception of patient 11, the majority of participating patients had lived with their illness for a number of years and were further along the disease trajectory. This represents a limitation of the study as it does not capture the perspective of patients earlier in the course of their illness with palliative care needs, which were implicitly rather than explicitly managed by their usual care team. There are a number of reasons for this: patients are not being formally recognised as requiring a palliative approach to care earlier in the course of their illness (GPRD study); the ethics committee requested that patients had to have had conversation(s) with their HCPs about a palliative care approach which may not have happened earlier in the disease trajectory and finally, few patient participants were identified by their GP, compared with day hospice staff and HFNSs. GPs are the group most likely to be managing palliative care needs for people with heart failure earlier on in their disease trajectory without recourse to either specialist palliative care services, or the HFNS, and who, from the interview data may not have made an explicit decision or had a discussion that this was the approach to care.

However, as the research gap is with regard to the experience of patients who are having a palliative approach to care (that is, there is now a considerable literature which describes unmet palliative needs for people with heart failure in general), these were unavoidable limitations due to the ethics committee stipulation. An attempt was successfully made to capture the experience of patients that were not managed by specialist palliative care services.

An additional limitation is that patients selected the health care professionals to be interviewed. Despite, research governance approval being in place for me to interview secondary care clinicians, notably cardiologists none were selected by patients. Cardiologists are an important group in the management of heart failure and this represents a missing perspective. Since the PhD the student has undertaken focus

groups with health care professionals including cardiologists to provide this missing perspective, and these findings will be reported elsewhere.

A vital question to consider is the transferability of the research and if it can inform practice? Qualitative research is not generalizable in the same way as quantitative research but may be transferable to other settings. Theoretical sampling[271] and descriptions of the setting and perspective can help readers assess their applicability to their own settings by a process called resonance[260]. This study may be less relevant to countries outside the UK if they have very different health care systems.

7.4 Reflexivity

Section 7. 3 above has focussed mostly on methodological reflexivity and the individual self-reflection of the role of the researcher will be discussed in this section. However, wider concerns also require consideration with regard to their influence on the research project. The ontological and epistemological, reflections were discussed in **section 5.3.** The historical, societal, political and philosophical influences were discussed in **section 1.2.2** and **section 1.3.**

As discussed in **section 5.3** reflexivity and the concept of researcher as research instrument is important, it is not about reducing bias but accepting and exploring the effects of multiple perspectives.

The decision to study this area was strongly influenced by clinical interest in the area of non-malignant palliative care and my experiences both as a palliative care doctor and as a junior doctor, prior to specialising in palliative care. Inevitably, although less directly relevant, my main supervisors have a strong clinical and research interest in this area. Professor Johnson was instrumental in setting up the integrated heart failure palliative care service[133]. At one level this was very important to have motivation and commitment to the research and clinical knowledge of the area. Arguably, it is a "Cinderella" topic, and even though it spans cardiology, general practice and palliative medicine there has been little clinical research regarding palliative care for patients with heart failure and so having the interest was important in meaning the research was conducted.

However, to some extent it meant I could have preconceived ideas or "bias" about the research and particularly the positive benefits of palliative care and had thus the potential to reduce the credibility of the research.

I was aware of this and specifically probed for negative findings with regard to palliative care I also looked for silences when positive effects were not discussed and deviant cases as discussed in **section 7.3.1** above. Interestingly as interviewer, even as someone who is very used to discussing end of life issues with patients and their families, I was surprised at how readily and quickly these patients discussed these issues, perhaps adding further resonance to the findings.

Another important area is to discuss if I was to introduce myself as a medical doctor or a researcher as it would influence the interaction between researcher and participant[293]. My participant information sheet (see **appendix nine**), described my current role as a PhD student as it was important the participants understood this was a PhD project. After review by a patient group, it was changed to refer to me by first name, to be more approachable. I therefore, went to the patients as a student researcher, but did not hide my professional role if I was asked about it. Some patients were informed by the recruiting teams that I was a medical doctor, for example stating I used to work at the hospice. One study has suggested that the interaction is more informal if the researcher is not a doctor[293]. Ultimately it is impossible to know the effects but it is important to be transparent about it. None of the patients were known to me and my clinical practice was outside the research area.

With regard to the HCPs, the majority, knew or asked by professional background and interest. This could have influenced articulation of perceptions in particular saying what they thought I wanted to hear. Many of the HCP were not know to me, others I only knew as a result of their help with study recruitment or if I had worked with them previously it was more than five years ago and I had not directly worked with anyone I interviewed.

I was also reflexive with regard to my influence in data generation. I went on two day in depth interviewing course at NATCEN. I listened to each of the interviews after they were conducted and considered my approach to interviewing. For

example, I was being encouraging but I realised this could be interpreted that I agreed with what they had said and so I endeavoured to encourage responses but in a more neutral way.

At times I was aware that the research was helpful for some participants as they were talking about their illness. This has been highlighted in the literature and I had anticipated that this might happen and included this in the participant information sheet (see **appendix nine**):

> *"What are the possible advantages of taking part in the study?*
>
> *Some people may find talking about their illness helpful. However, there is no specific advantage to you taking part in this study. We are carrying it out to see if we can help the care of patients with severe heart failure in the future."*

However, what I felt uncomfortable with was that some participants were directly comparing the research interview to interactions with their HCPs

This quote was in response to a question about communication with the HFNS.

> *"…but we don't get as intimate as what, what we've got with you. But we're releasing, I've been releasing details out that I wouldn't do and it's, it's nice to get rid of it really, and let someone else know how I feel. But I've never been able to do that with HFNS, not properly, but there it is. And so I'm stuck with it Amy, and I'm doing me best to get out of bloody way but I can't. (laughter)" (patient 11)*

This is an important finding not only because it resonates with previous research finding about the potential therapeutic benefits of taking part in palliative care research for some participants[294].

I was concerned about the unmet need of this patient, with regard to communication, despite having a palliative approach to his management. There were other examples of this, for example, a patient clearly articulated that she wished to die at home, however had not mention this to her HCPs. I had to recognise however, that this was an important finding. I encouraged her to speak to her health care team about this conversation.

Perhaps, the main reason why I felt uncomfortable was because of my concerns about separating my role as researcher and that of my clinical role as a palliative

medicine doctor. Although, I had considered reflectivity and specifically my role in influencing the research project I had not considered its influence in such a direct and potentially therapeutic way. It is not possible to totally separate the two roles; but it is important to remain vigilant to their influence by reflexivity.

7.5 Joint interviewing of patient and carer participants

Another decision was regarding joint patient and carer interviews or keeping these separate. I decided to give patients and carers the choice regarding if they wished to be interviewed together or not. This was in order to be patient centred and allow participants to take part in a way that was comfortable for them. Asking carers or patients in their own home to be interviewed separately can be ethically difficult[294]. One researcher has suggested that about half of palliative care patients prefer to be interviewed jointly[274]. There is concern that this can constrain the discussion but it may also allow patients and carers to prompt each other to mention or expand on issues. This was evident in this research project[294, 296]. My impression was the option of joint interviewing encouraged participants to take part in the study, whereas they would have been reluctant to be interviewed alone. One study has investigated this and found it does increase recruitment[296].

In a study in which it was vital to gain an individual's perspective other techniques could be used. This could include two researchers interviewing the patient and the carer at the same time or conducting both joint and separate interviews, although that would place an additional burden on patients and carers[296].

7.6 Applying for research ethics approval for research involving palliative care patients

7.6.1 General overview of health care research ethics

Following from Nuremberg (the doctors' trials) 1946-7, which highlighted atrocities of medical experimentation undertaken by the Nazi regime the Nuremberg code was published in 1948. This outlined ten points that define legitimate and ethical medical research, prior to this there was no generally accepted code of conduct governing the ethical aspects of human research. In 1964 the World Medical Association published the Declaration of Helsinki. This was based on the Nuremberg code and it underwent its sixth revision in 2008[296, 297]. It has been described as the most widely accepted guidance worldwide on medical research

and although it is not legally binding it has had significant influence on individual countries legal frameworks[296]. It is not without its controversy and the US has not signed up to its latest revision.

Good Clinical Practice (GCP) is an international quality standard for clinical trials, although many of the principles are relevant for other types of research on humans. It has been incorporated into UK law in "The Medicines for Human Use (Clinical Trials) Regulations 2004"[298]. In England, the research governance framework is the guidance for the appropriate conduct of all research not just clinical trials and the devolved nations have a similar framework. The majority of human research undertaken in the UK requires legally or as a policy requirement review by a research ethics committee, the National Research Ethics Service (NRES). In May 2011 they produced updated guidance as to which projects require review by Research Ethics committees (RECs)[299]. RECs are independent committees composed of up to 18 members; a third should be lay representatives. Their role is to protect the dignity, rights, safety and wellbeing of research participants[300].

7.6.2 **Why do we need research in palliative care and specific concerns?**

The reasons for research in palliative care are the same as for health service research in other fields, to improve the care of patients by providing evidence of the effectiveness of the treatments and care we provide. It has been argued that not carrying out research in this group of patients is unethical as it leaves patients open to futile or useless treatments and because of lack of evidence of effectiveness they are then exposed to being unwitting participants in "n of 1" clinical trials by default, without their explicit consent[301]. It is important to differentiate between research in palliative care patients, which is involved in improving the care of patients at the end of their life and phase I trials in the terminally ill, often those with no further anti-cancer treatment options. These trials, for example of chemotherapy, are designed to explore dosing and side effect profiles, not effectiveness. This will happen in later phase II or III trials, and so are not likely to have benefit in an individual participant. However, despite this research has shown that patients involved in these trials did so thinking they would have therapeutic benefit. This has led to claims of exploitation of the terminally ill[302].

Those at the end of their life are often seen as a vulnerable group. They may: fatigue easily; participation in research may use time and energy away from family or "unfinished business" and concerns about coercion as they are very dependent on their clinical teams. They do not personally benefit from the research that is being undertaken and there are issues of fluctuating capacity and or a rapidly changing condition[303, 304].

However, it has also been argued that many of these barriers are similar to ethical issues in other patient groups and are not insurmountable or requiring special ethical consideration, beyond the essential ethical considerations required for research in all patient groups and well described in the international and national guidance and legislation described in the earlier section[303, 304].

It is contested if palliative care patients are a vulnerable group or this is a paternalistic view. Many concerns have been expressed about gate keeping by clinical staff and ethics committee with regard to palliative care patients. It is argued that palliative care patients have a right to be asked to be involved in research and the autonomy of the patients themselves to make their own decisions should be respected[294, 303, 304]. There is growing evidence that palliative care patients do want to be involved in research and want to be able to decide themselves if they wish to be involved or not[294, 305-308]. Research exploring hospice patients views regarding being involved in medical student teaching has highlighted similar themes[309].

7.6.3 **Specific ethical issues with research project**

When planning this research I considered carefully all the ethical considerations highlighted in national and international guidance such as consent and confidentiality. These were then presented to the Research Ethics Committee and approved; this is not going to be discussed further in this section.

However, there was a specific concern, I thought very carefully about how I would present information to patients. Specifically I did not want to be giving any new information or cause unnecessary distress to participants. I was particularly conscious that my role was as a researcher not a clinician. In my clinical role I do have conversations with patients and their families about their limited prognosis and the change in their care. For the participant information sheet, I decided to use the

words: "severe heart failure" "further difficulties" and "change in care" rather than palliative care.

Within the interviews themselves because of the method of data collection, the semi-structured interview, I could reflect the language the patient used. As well as the ethical importance of not presenting new information to the patient, it is also important for the research to allow the patients' views to come across rather than be unduly influenced by the researcher. My clinical training, for example, when talking with patients, begins with gaining an idea of what the patient understands about their condition, and my training in interview skills for the research project meant I was comfortable with this approach; my concern was with how to present information in a written form to a patient who you have not met.

The protocol including all the participant information sheets were reviewed by a local consumer research panel, patients (cancer, heart failure and other chronic illnesses) and their carers who have an interest in research.

Ethical dilemmas are often compounded by difficulties in communication. Palliative care as discussed in **section 1.2.1** is defined as:

> *"An approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness…..*
>
> *….is applicable early in the course of illness, in conjunction with other therapies that are intended to prolong life…"*[1]

However, what does the term palliative care mean to patients or even HCPs? It is also compounded by changing or different terminologies such as end of life care, terminal care and hospice care[46, 310]. Palliative care may be perceived as, withdrawal of treatment, imminent death, cancer patients or referral to another service such as a hospice. However, as the above definition illustrates, none of these are included in the definition but the concern is that this is often the perception.

The difficulties in terminology and communication about palliative care may reflect difficulties in society with discussing death and dying. Palliative care, especially specialist palliative care, is often associated with "open awareness" where issues of prognosis are openly discussed between patient and HCPs and patients are

prepared for their approaching death and is seen as a challenge to society, where these issues are avoided[23]. However, these polar views are overly simplistic. For individual patients the level of "awareness" varies over time and some patients may never wish to consider their prognosis, and others may never have been given the opportunity. However all of these patients may still be having a palliative approach to their care as defined by the WHO. This project, by its nature of exploring non-cancer palliative care patients, where it is known there are communication difficulties in discussing palliative care and looking specifically at the time of changing care, means that the communication is particularly challenging.

7.6.4 Review of literature regarding presenting palliative care research to patients

The general research literature regarding research ethics and palliative care is discussed in the **section 7.3.3** above. Three papers discussed this specific concern of how to present information about palliative care research to patients[304, 311, 312].

The concern that palliative care can be emotionally laden to some research participants is discussed in a paper by Addington-Hall in 2002. She suggests that even in specialist palliative care, some participants may not be used to this term or find it distressing and even more care is needed in non-specialist palliative care settings. She recognises that participants do need sufficient information to make an informed decision[304].

A more recent paper, describes difficulties a research group had in applying for REC approval for a mixed method study about palliative care for patients with COPD. They were advised by the REC that there should be no mention of palliative care, end of life or even COPD as the participants might not know their diagnosis. They were concerned that the balance to protect participants from potential harm due to terminology meant that they were unsure if participants could be truly giving informed consent to be involved in the research[311].

However, another research group, used the phrase "become more unwell" rather than end of life or dying in their participant information sheet of patients who had been identified as potentially so unwell that their treating team felt they could die during their hospital admission. The research group's reasons included they did not want the information sheet to put off HCPs from recruiting the patients and they

do not want patients to find out they were potentially dying, from a patient information sheet[312].

7.6.5 Ethic committee response and changes made

The initial response of the REC to my application was:

> *"They (patients) should be fully aware they are receiving palliative care the terminology should be honest. There must be a cut off between curative and palliative care and this must be communicated to patients by clinicians and in this case researchers."*

With two further submissions the application was approved, palliative care is not mentioned in any participant information sheets, including for HCPs. It does not include any idea that there should be a cut of between curative and palliative care.

The eligibility criteria for patients have been strengthened to include that a clinician had conversation(s) with patient about the change in approach to their care.

The participant information sheet (**see appendix nine**) now includes:

> *"You will have had a conversation or a number of conversations with a doctor or nurse about understanding that cure or full control of your symptoms is unlikely to be possible and changing the focus of your care to helping minimise the impact of your symptoms and offering more support to you and your family."*

7.6.6 Conclusions regarding applying for research ethics approval for research involving palliative care patients

I initially felt that the REC did not understand my project and the nature of palliative care, especially for non-cancer patients and I was therefore, concerned that making changes would lead to a poor research project. However, making changes due to RECs response, in some ways strengthened it. And by making patient selection clearer, it answers more appropriately my research question.

The more pertinent question is, is it ethical research? I set out to undertake ethically sound research. This area is difficult but not researching this area is also ethically unsound. The inconsistency of response from ethics committees reflects difficulties in the subject itself, for individuals, for HCPs and for society. There will continue to be tensions between protecting individuals and allowing participation, which rightly requires understanding of the research project. The patients I have

interviews have strongly resonated that they want their voice to be heard and openly and readily discussed the research question.

7.7 Methodological issues with regard to recruitment

Recruitment may be difficult in palliative care populations and poor recruitment is often cited as a reason for inadequately powered trials or failure of studies[312]. In this study a particular challenge for recruitment was the purposive sampling of patients with heart failure and a palliative approach to management: a limited population of potential participants. There are numerous factors influencing recruitment and these can be divided into patient factors such as frailty and those related to health care systems (e.g. gatekeeping by HCPs)[212, 294, 309, 313, 314].

Patients and health care system factors were considered in the study design and conduct of this study to aid successful recruitment.

Patient factors included: a one off interview (reduced burden for patients and reduced problems of high attrition rates); at a place convenient to patient (generally home); opportunity to be interviewed jointly with carer and the ability to indicate verbally to the team that they were happy for researcher to contact them (rather than fill out a form). Another factor was allowing joint interviews, my perceptions is that this encouraged participation not only in the interviewing by prompting discussion (see **section 7.5)** but may also have aided recruitment in participants who may have been apprehensive about being interviewed alone. It has been suggested that joint multi-perspective interviewing can aid recruitment as it moves carers from being protective gatekeepers to participants[274]. Health care system related factors included: a multicentre study even though I only recruited 19 patients, which required nine different research governance or institutional approvals including honorary contracts or letters of access. Two of the hospices had taken part in research before and so had some experience of approaching patients to consider taking part in this research. The patient factors were also important to HCPs involved in identifying patients to reduce gate keeping.

The research topic was of interest to the HCP that identified patients. For example all the HFNS teams were very interested in palliative care, even those teams with less clinical experience with palliative care for patient with advanced heart failure. HCPs has their own different, individual reasons for wanting to be involved in

research, for example, one day hospice team was interested in showcasing their involvement in research to hospice trustees.

I perceive that a significant factor, in conjunction with recruiting via many different teams, was spending regular face to face time with each of the teams. I developed good relationships with each of the teams for example, I conducted teaching sessions. Gate keeping was not a particular problem as illustrated by the number of potentially eligible participants that took part (see **figure 16**).

Although it took time, both in applying for multiple research governance and institutional approval and the time I spent with each team, the recruitment for this study was good and I was able to complete recruitment of patients ahead of schedule.

Health care recruitment was also good, with only two out of the potential 19 HCPs not able to take part in the study. One GP retired and so was not be able to be contacted (although the patients second choice HCP was interviewed instead) and one GP declined due to work load pressures, secondary to staff shortages. There is less literature regarding recruitment of HCPs to studies but it is suggested HCP recruitment in multi-perspective interviewing is generally good[274]. This is certainly reflected in my experience and it may reflect the personal nature of the invitation to take part in the research. I was very flexible with regard to place and time of interview and needed to contact some HCPs multiple times to organise interviews. It was also helpful to use different modes of communication, email, telephone and letter. Overall, however, I was surprised at the willingness of busy HCPs to be interviewed.

One group where recruitment was potentially less successful was recruitment of carers with 11 out of potentially 17 potential participants (two patients were not able to identify any carer). However, this is in line with the literature in this area that this can be a difficult group to recruit[274, 292]. Carers have a high burden of caring responsibilities and so may have little time. It also is a difficulty of labelling as people see themselves as the patients spouse or friend rather than carer[292]. Due to the nature of how these carers were recruited (via the patient) it is difficult for the researcher to influence the process beyond good participant information leaflets,

clear communication with patients and flexibility regarding place and time of interview.

7.8 Summary

The ability to critically assess the strengths and limitations of research is a vital skill for a student researcher. For qualitative studies the issue of reflexivity is an additional requirement. Important lessons may be learnt by reflection on methodological issues such as ethics and recruitment, which will be helpful in planning future studies.

Ethics committees may have a poor understanding of palliative care, for example, that it was an either or approach, which could be a barrier to receiving necessary ethical approval for palliative care research. As a researcher, this means you have to be clear about your patient population and how you describe them. Interesting it is the same barrier that is present in clinical practice.

A strength of the study was the multi-perspective interviewing that aided recruitment and provided rich data that had the potential to change clinical practice as the patient, carer and HCP perspectives on the same issue was present[274]. Further insights into this important area can be made by integrating the findings of all the studies presented in this thesis and this will be the topic of the next chapter.

8 Synthesis of research findings and discussion

8.1 Introduction

This thesis has addressed the issue of palliative care for people with heart failure. A systematic literature has explored variables associated with the last year of life. GPRD has explored recognition for the need for a palliative care approach in patients' with heart failure in general practice and the qualitative study has researched the perceptions of patients, their carers and HCPs who have a palliative approach to their care. The individual findings have been discussed in the appropriate chapters. However, the findings are all exploring different aspects of the same research question and by integrating the finding the aim is to create new understandings that are greater than the sum of its part[315].

The chapter will begin with a general introduction to mixed methods research and detail the method of integration used in this thesis, followed by the findings and conclude with implications for research, clinical practice and policy.

8.2 General discussion regarding mixed methods research

Mixed methods research can be defined as:

> *"design for collecting, analysing, and mixing both quantitative and qualitative data in a study in order to understand a research problem"*[316]

The use of multiple methods reflects an attempt to secure an in-depth understanding of the phenomenon in question. They are particularly useful for enquiry into a complex area. Objective reality can never be captured (**section 5.3**) Triangulation is not a tool or a strategy of validation. The combination of multiple methodological practices, empirical materials, perspectives, and observers in a single study is best understood as a strategy that adds rigor, breadth, complexity, richness, and depth to any inquiry. The term crystallisation is often used instead of triangulation to emphasise that the mixed method approach is not confirming findings, but studying a problem using different methods to gain a more complete picture[316, 317].

There are various approaches to mixed methods research strategies. As with all research strategies it is primarily driven by the research question but also by theoretical and practical considerations such as time need to be considered[315].

Creswell describes four main considerations that influence the design of a mixed method study:

- Timing: the timing of the data collection
- Weighting: priority given to the quantitative or qualitative work
- Mixing: when (e.g. data collection, analysis) and how
- Theorising or transforming perspective: if a larger theoretical perspective guides the entire design[318].

The concurrent triangulation strategy is a common mixed method strategy in which studies are conducted separately and findings are integrated[317, 318]. The qualitative and the quantitative studies have similar weighting and there is no specific theorising perspective[317, 318]. This is the method used in this thesis, in part due to the very practical reason of the duration of the PhD fellowship, as sequential methods require more time to complete. However, despite this, some sequential integration at the level of data collection was possible. For example, once the results from GPRD became available, this raised specific areas that were explored in the qualitative interviews with the HCPs. These areas included: why were patients dying from heart failure much less likely to be put on GSF register, if they were, why were they placed on the register so late in their disease trajectory, and, were there concerns about the consequences of early identification and registration? The systematic literature review defined specific clinical variables that were included in the GPRD study.

8.3 Method of integration used in this thesis

Returning to the research question:

To explore a palliative approach to care for community based patients with advanced heart failure: recognition of need, transitions in care and impact on patients, family carers and clinicians

The synthesis of findings from the quantitative and qualitative aspects of this thesis has been approached in two stages. Firstly, aspects of the research question have been taken and comparisons drawn from the findings from the systematic literature

review, qualitative and quantitative studies pertinent to each aspect. Summary findings for each section of the research question are then given. These are presented in tabular form in **table 27**. The new insights gained from the integrated findings will be presented (**figure 24**) along with their implications for clinical practice, future research studies and policy.

8.4 Synthesis: findings of a mixed method study

Table 27: Summary of the mixed methods with integration of findings across aspects of the research question

	Background literature	Systematic literature review	GPRD	Qualitative study	Integration
Definition of "palliative approach to care"	Distinction between: generalist palliative care specialist palliative care palliative approach to care (broader includes both)	Cannot currently define by prognostic variables Participants in studies often selected population (for example elderly patients and those with co-morbidity excluded)	Data does not give details of: generalist or specialist palliative care or broader palliative care approach; but marker of recognition of the need for a palliative care approach Elderly population many with co-morbidity	Purposive sampling of patients where palliative care approach implemented; some accessing specialist palliative care, some general palliative care communication and teamwork important	Generalists and specialists have important roles – with complex interplay. Communication and team work important in recognition and transition Patient plays pivotal role Elderly population with comorbidity, not often represented in studies of prognosis
Transition to palliative care approach	**Impact** Poor referral to general and specialist palliative care **Barriers** Recognition of advanced disease Team concerns about taking away hope and "getting it wrong" Societal and professional understanding of palliative care and heart failure Fragmentation of care **Policy facilitators** Prognosis (last year of life) **Proposed facilitators from existing integrated services:** Needs based	**Impact** Many prognostic variables, but none seem helpful in recognising last year of life **Policy facilitator** of recognition based on last year of life now **barrier** therefore need to overcome other barriers such as communication or use other proposed facilitators such as a need based approach **Future facilitators** Appropriately designed cohort studies of prognostic variables	**Impact** Heart failure patients poorly represented on the palliative care register, and those that were, were registered close to death. Potential reason for differences in care compared with cancer patients **Barriers** Prognostic variables not used as decision to place on palliative care register **Facilitator** Some heart failure patients with palliative care approach may not have been placed on palliative care register, see text	**Impact** Recognition and transition to palliative care approach is possible for the patients with heart failure Transition opens up access to helpful services and opportunities to enter into joint decision making which improve QoL for patient and carer **Barrier** Clinicians reluctance to discuss palliative care approach unless irreversibly deteriorating Symptoms more of a concern to patients than HCPs **Facilitators**	**Impact** Poor recognition of palliative care approach but can be overcome; delay in initiation of conversations may delay or even prevent access to useful approach/service **Barriers** Prognostication based on last year of life HCP delaying/or never initiating communication HCPs understanding of trajectory Poor engagement by the HCP with patient concerns about symptoms **Facilitators** Patient and carers wish for palliative care approach and

				Patients and carers may recognise and wish to discuss palliative approach Palliative care approach for periods of stability or improvement (months to years) considered appropriate by HCPS and patients, in fact welcome periods of stability	ability to communicate this to HCPS For the future appropriately conducted cohort studies of prognostic variables, may be helpful as an additional aid to discussions and decision making about future care
Implementation of palliative care approach	**Impact** Increasing evidence that early palliative care recommended in oncology In cancer: Improve QOL patients and carers Improve advance care planning (for example rate of home death, potential for timely deactivation of ICDs in cardiology) Improved communication within families, between clinician and patient and between health care teams (co-ordination of services) ? Reduction in health care cost **Barriers** Specialist in palliative care concern about being overwhelmed with referrals **Facilitators** UK policy promoting	**Impact, barriers and facilitators** Implementation using prognosis trigger of last year of life not possible with current knowledge	The effect (**impact, barriers and facilitators**) for patients, carers and HCPs of being on palliative care register, not explored in this study, see text, but the late registry of HF patients compared with cancer patients has implications for potential unmet need	**Impact** Hope not destroyed by open conversations Supporting patients with their own coping mechanisms (patient centred) HCPs relieved once recognised and led to coordinated, proactive care Some unmet needs remain Needs based allows that some patients may have more than a year, but still have significant problems which may benefit from a palliative approach – see about stability **Barrier** General practice often reactive care, whereas palliative care aiming for proactive care Complexity of medical treatment and co-morbidly	**Impact** access to services, access to ACP and proactive care, appropriate goals of care, improved QOL and support for carers palliative care approach by promoting patients coping mechanisms may help maintain hope. Improved co-ordination of services **Barrier** Barriers can be overcome HCP concern about patients losing hope not realised in this population Some unmet need still remain

	palliative care for heart failure Prevalent disease with poor prognosis and high symptom burden			add complexity to HCP teams and may distract from discussions about focus of care Poor communication between primary and secondary care aggravating primary care reluctance to discuss change in focus of care **Facilitators** Need for monitoring and treatment adjustment may facilitate relationships and proactive care	

Table 27. Summary of the mixed methods with integration of findings across aspects of the research question.

ACP=Advanced care planning

8.4.1 **Definition of palliative care**

The systematic review that discussed the definition of a palliative care population (**chapter one**) emphasised the importance of a shared understanding of palliative care by the patient and all caregivers, both informal and formal[9]. This vision appears to be missing in current policies which focus on prognosis as the *primary* trigger to identify patients who need a change in approach to care to one of palliation. Only once this has been agreed can the patient then start to be managed in this manner. Several patients in this study initiated conversations about change in a focus of their care themselves, when clinicians were hesitant. A return to patient centred care in policy would facilitate these important conversations about change in focus of care that appear to be appreciated by many patients and carers. This will allow patients the opportunity to discuss matters of importance to them (such as symptoms – a feature strikingly absent from the HCP narratives) and restore their own coping mechanisms.

A commitment to keep the patient as the defining focus of palliative care is central to public health initiatives in palliative care, such as Dying Matters[319]. These initiatives encourage individuals to discuss issues relating to death and dying with their loved ones and HCPs. Whilst providing a helpful signal to patients that they can discuss sensitive topics, the overall responsibility for initiation of such conversations about the palliative phase of the illness should not lie with the patient or carer. We should welcome patients who wish to start the conversation about end of life issues but the primary responsibility lies with the clinician. The GMC guidance is clear; clinicians should be discussing end of life issues with all patients, who wish to, who are expected to die in the next 12 months[41]. This is described very eloquently by patient 14 in the qualitative study. She was surprised when she was told she potentially had a poor prognosis, but she had asked because she wanted to know and felt it was the responsibility of the doctor to tell her. She also felt it should be done in such a way as to maintain hope, not by lying, but by the clinician's sensitive approach and use of excellent communication skills.

Palliative care, generalist palliative care and specialist palliative care are defined in **section 1.2.** The broader term "a palliative care approach" (**section 2.6**) encompasses all three terms and was therefore deemed most useful for this thesis. The usual clinicians caring for the patient, who may be a primary or secondary care

practitioner, provide generalist palliative care – that is, provision of palliative care is not their core role. They are therefore, as primary contacts, clinicians who i) identify patients who need a palliative care approach ii) initiate, or respond to, the discussions about the need for a change in approach to care and iii) lead the process of advance care planning. This is different to the specialist palliative clinician – for whom palliative care is their core role, who have additional training and experience and who will therefore see patients with complex or persistent palliative care needs. However, they can only provide this service for patients i) once the need for a palliative approach has been recognised by the primary clinician, ii) the primary clinician has addressed the issues as well as they can and iii) the primary clinician recognises that the patient may benefit from a referral to the specialists. The integrated findings across the different studies in this thesis show a complex interplay between generalist and specialist. Generalist clinicians find timely identification of patients and the initiation of conversations about palliative and end of life care difficult. However, once a palliative care approach to care has been agreed between clinical team, patient and carer, such an approach to care leads to benefits for the patient and carer, and the clinicians' concerns about implementation resolve. This raises the question of how the role of the palliative care specialist should be optimised to support the generalist with this challenge and solutions may include a greater involvement of the specialist in the identification of patients who need a palliative care approach and to implement assessment of and attention to palliative care needs. Closer working between generalist and specialist will also increase the palliative care knowledge and skills of the generalist, which may lead to highly appropriate referrals as the generalists gain a better understanding of their own skill limits, and of how a referral to specialist services might benefit the patient.

Integration of results from the systematic review, GPRD study and the interview also highlighted that the vast majority of the prognostic studies had limited relevance for the many patients with heart failure seen in daily practice who include the frail elderly with multiple co-morbidities. Thus it is unsurprising that the review did not find clinically useful markers of the "last year of life", and neither did the prognostic studies contribute to an understanding of a definition of palliative care despite their purport to identify those with poor survival.

8.4.2 **Transition to palliative care approach**

As discussed above, the focus on prognosis provides a barrier at the start of the process of access to a palliative approach which may include, if needed, referral to specialist palliative care services. This barrier is complex. The main features arising from the synthesis of results will be discussed under the following headings.

An erroneous understanding that palliative care may only be appropriated for patients with irreversible and clear deterioration over an expected timescale of a few months

The Department of Health commissioned palliative care funding review described four phases in a patient's illness: stable; deteriorating; unstable; dying. This provides an important emphasis for the observed non-linear nature of the phases which can be repeated and are variable in length. Periods of stability and even improvement can and do occur in palliative care. If there is poor understanding of this phenomenon, and clinicians or patients only recognise the need for palliative care when there is certain evidence of irreversible deterioration, then a barrier to recognition and transition is created. This was a clear theme in the qualitative data, and interestingly, when periods of stability were observed despite a palliative approach to care, clinicians could see that this, of itself, was not a problem in providing on-going care using a palliative approach. This need for clinical "certainty" may be an explanation for the late placement of patients dying from heart failure on the palliative register in the GPRD study. Likewise, interviewed clinicians that agonised over the decision to initiate a discussion about palliative care, for fear that the prognosis was not yet bad enough, could see that once the discussions had led to a transition to a palliative care approach, then this had not been a valid reason for procrastination, even if the patient subsequently had periods of stability or even improvement.

An erroneous assumption that palliative care in cancer is only accessed by patients with irreversible and clear deterioration over an expected timescale of a few months and therefore the same pattern should be followed in non-cancer palliative care

In the UK, most palliative care is integrated within the cancer pathway. Specialist palliative care services have grown, for the most part, within oncology services. Initially, the traditional model was used of active treatment followed by handing

over to primary and/or palliative care services once active treatments had ceased and as performance status worsens. However, over the past 20 years at least, as cancer treatments have made many cancers mirror chronic conditions, the services in the UK have adapted to follow an integrated model. Cancer patients have fluctuating symptoms and performance status. Palliative care services may therefore be accessed intermittently in response to particular problems earlier in the disease (often with a good performance status), leading to increased involvement as the disease progresses[116]. However, in spite of this, the concept of a palliative care population as one with clear irreversible decline persists, rather than one of a transition of approach. The fluctuating trajectory of non-cancer conditions such as heart failure is therefore still seen as a barrier to recognition. The lack of a clear-cut stage where all disease directed treatment is stopped is used as a reason why clinicians do not know when to refer to palliative care, even though extended integrated team working works well for oncology palliative care.

Possible contradictions in HCPs treatment of cancer and heart failure patients with regard to the palliative care / GSF registers

The formal recognition by primary care teams that a patient now requires a palliative care approach by placement on a palliative care register appears to be clinical common sense to: provide a consistent approach to care; ensure an assessment of symptoms and other needs; start advance care planning; co-ordinate with other care services. In general, palliative care registers have been well received and most practices in the UK now have a Gold Standards meeting at least every three months as a result of Quality Outcome Framework requirements[320]. However, implementation is variable, not only with regard to implementation or not, but with regard to the effectiveness and completeness of the implementation. For example, some practices hold palliative care meetings every week, others every month, and still others at the minimum requirement of every three months. Engagement from practice staff is variable, and the direct impact on patients and carers is not known[320].

Despite lack of robust evidence of benefit, palliative care registration is nonetheless a reasonable marker for patients who have been identified by primary care practitioners as being those where a palliative care approach is now appropriate.

The qualitative study did have data to suggest that some HCPs may identify heart failure patients as needing a palliative care approach, but did not place them on the palliative care register. Cancer patients seemed to be placed on the palliative care register "more automatically" than heart failure patients. However, that in itself is an inequality, denying patients the explicit multidisciplinary care plans arising from team discussions at practice GSF meetings. It is also interesting to reflect on how the decision to place cancer patients on the palliative care register did not seem to be due to prognostic variables, including the "surprise question", but rather that the cancer patients were more automatically considered for the register. Those patients that were discussed at GSF meetings were those with increasing care needs such as district nursing needs. A similar finding is found by a Scottish study that examined palliative care registers in six GP practices[234].

However, the fact that registration, if it occurred, for people with heart failure was only done in the last week of life, and there was such a gross discrepancy between heart failure registrations and cancer registrations for palliative care, makes it unlikely that the deliberate non-placement of heart failure patients on the palliative care register is a major contributory explanation for this inequity. Additionally, late registration or failure to place on the palliative care register is an inequity in itself as patients would not be discussed at a GSF meeting. In addition, the overwhelming theme with this regard from the HCPS interviews was one of procrastination, rather than recognition and use of alternative ways of implementing a palliative care approach. HCPs were asked about their usual practice with regard to palliative care for patients with heart failure and apart from one HFNS and two SPCP (all three from Scarborough, with an integrated palliative care service) it was not part of their routine practice.

Emphasis on "when" facilitates advance care planning. However advance care planning conversations can be difficult for HCPs and some patients

As has been discussed, UK policy on "end of life care" has a particular emphasis on *time.* If patients are in the last year of life, they can have a plan of care and a discussion about where they would like to die. Although most of the participating patients in the interview study described the importance of realistic planning for the future, some recognised that this was not a pleasant or easy topic. In keeping with

the literature summarised in **section 1.6.2** data from the HCP interviews agree on the importance of truth telling but find discussions about future care difficult. Although many admit they have recognised that a patient has end-stage disease, there was still a need to be certain and perhaps at some level they were avoiding the difficult conversation. This could be a potential concern even if better prognostic markers are found and validated in the future as they would never be 100% accurate and so a degree of uncertainty would always be present. As discussed in previously in **section 1.6.2** and **section 3.6.7** prognostic information needs to be communicated and acted on. Also some patients cannot deal with these difficult conversation(s) straight off, but they still have symptoms that need to be dealt with and this time can be taken to build trust. An example of when this was required is patient 12 (**section 6.3.2**).

Conversations are difficult but necessary and often welcomed by patients

Uncertainty should not prevent exploration of patients' wishes about the focus of their care and the approach to care was felt by all participants in the qualitative study to be beneficial even in those who stabilised or improved. The HCP's major fear of taking away hope was not realised, as hope was reframed, if necessary, to achievable goals that were identified as important by the patient and carer. Thus clinician fear/discomfort should not be a reason for a clinician putting off an exploration of what the patient wants to know in the context of a review of their condition and planning for the future (using plan a and plan b approach – "hoping for the best, planning for the worst")[81, 126].

Patient factors: symptoms as a focus for transition rather than prognosis

It was interesting that planning was a strong theme for HCPs; and seemed to be a major worry, whereas the content of much of what patients and carers talked about was about symptoms, and their effect on daily life. Therefore, if HCPS assessed and addressed those that would lead to a discussion of relevant appropriate treatments, and what is likely to have benefit at this stage of the condition, which should naturally lead into conversations about ceiling of medical therapy, appropriate place of care, and increasing likelihood of futility of other

interventions – thus planning is addressed even in those who are not able to talk about prognosis.. The risk is, if HCPs put off the conversation because they think it has to be rooted in prognosis – i.e. what *will* happen, that the symptoms that the patient are experiencing *now*, will not be addressed in a systematic manner. Most specialist palliative services, as discussed above operate an integrated service model, even in cancer, therefore, referral for symptom management can still be done even if a patient is not yet in the "last year of life" with it . A bald diving in about prognosis is not only difficult, but can seem inappropriate. However, starting with what the patient is troubled with *now* starts a patient-centred discussion, which is likely to lead to an in context conversation about possible management plans.

It is important to emphasise that symptoms are not just physical symptoms, for example social isolation was a major concern in the patient interviews.

A recent editorial has proposed that palliative medicine's success in treating pain, with its attendant practice of holistic care and multidisciplinary team working led to its integration within cancer services. The editorial proposes that a similar approach with other symptoms such as breathlessness may have similar effects[321] and perhaps could integrate palliative care within cardiology and general practice for patients with heart failure.

At the integrated heart failure and palliative care service in Scarborough, specialist palliative care provide the necessary support and training to allow HFNS to develop communication skills which allow discussion of present needs and future concerns, despite remaining prognostic uncertainty. The HFNS are able to discuss any patient they wish at a joint multidisciplinary team meeting and specialist palliative care will see patients as required. In this example of joint team working, the HFNS are able to discuss future plans as part of the overall management, and these include explicit conversations about preferred place of death[57, 98].

8.4.3 **Implementation**

Patients described access to communication, decision making, support and services which helped their quality of life and helped restore their own coping mechanisms. HCPs found the united aim of care useful. It therefore is disturbing that of the seven per cent of patients with heart failure on the palliative care register, a third were registered only within the last week of life. It is highly unlikely that these

patients only developed difficulties in that last week. Thus, delay in recognition results in patients and carers being denied the opportunity for valuable help at an important stage of life.

The complexity of heart failure treatment highlights the need for a multidisciplinary approach to care and is another reason why the model of transfer to specialist palliative care as a patient is irreversibly deteriorating is inappropriate. Communication between team members in the qualitative study was described as good, however, there was still the potential for things to be missed or tasks to be repeated. Therefore, clear communication is needed, perhaps in a planned way, for example, regular face to face meetings and written communication to all, especially the GP, rather than the more *ad hoc* methods of communication described in the qualitative study.

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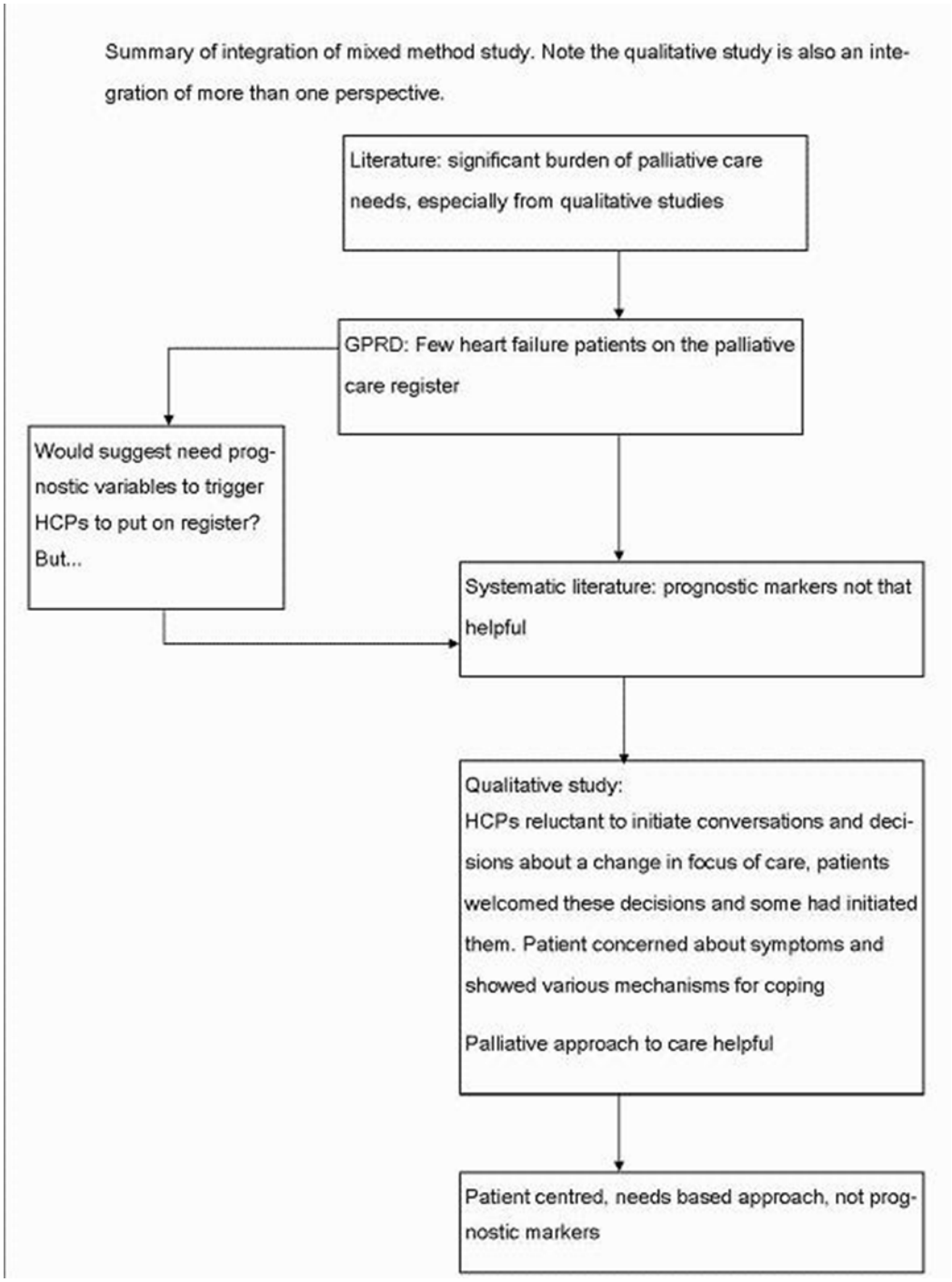

Figure 24. Summary of integration of all the studies and new findings that were greater than if conducted individually

8.5 Strengths and limitations of the mixed method study

The qualitative study was particularly useful to fill in the gaps of the quantitative research and to provide explanatory data for the quantitative findings (both GPRD and systematic literature review). The GPRD study was able to put the findings of qualitative background literature described in **chapter one** into a much broader context; confirming that the inequity of access to palliative care described in interview studies is a feature across the whole nation. Data for crystallisation was not possible for all areas of the research question. For example, the integration was weakest for the aspect of the research question that explored implementation and often there was only qualitative data available. Implementation should be explored further by different studies, for example by trials of effectiveness.

More general considerations with mixed methods are that time and resources are split among multiple methods and so they are less in depth than if just one method had been focussed. It can also be difficult if to know what to do if there are discrepancies between methods, which was not a particular problem in this study[315, 316]. Multiple methods can be useful training in different research designs for a student researcher.

8.6 Implications for clinical practice

- Systematic regular assessment of symptoms and other concerns experienced NOW by patients and carers
- Consider all patients on GP heart failure registers, all patients identified by NICE quality markers for heart failure which include requirement for holistic assessment at times such as discharge from hospital[42] or all patients on a HFNS case load
- Support by specialist palliative care for HCPs providing generalist palliative care by:
    - Increased profile in teams prior to patients being referred such as attending multidisciplinary team meetings or outpatient clinics
    - Education regarding basic symptom control, need for regular proactive holistic assessment (including psychosocial carer and information needs) communication skills, especially with regard to uncertainty and role of palliative care (patients do not need to be irreversibly dying, and may improve or stabilise)

- Clear communication (preferably written and or face to face) between cardiology, primary care and specialist palliative care regarding focus of care for an individual patient
- Support patient initiatives such as Dying matters[319]
- Re-structure services in both primary and secondary care to allow time for patient centred discussions

8.7 Future research

8.7.1 Prognostic markers

Chapter three the systematic literature review concluded with descriptions of possible future studies of prognostic variables in heart failure including, measuring variables over time and using cohorts that represent clinical practice.

8.7.2 GPRD in palliative care research

Chapter four used a successful method that could be used to further interrogate the GPRD to explore the recognition of the need for a palliative care approach for other diseases such as COPD. The GPRD could also be studied to explore if any prognostic variables were recorded in GPRD around the time the decision was made to put a patient on the palliative care register. The qualitative study also included focus groups with different groups of professionals in primary and secondary care to allow a broader range of professionals' views to be collected. This data was not presented in the thesis but will be analysed and presented elsewhere.

The thesis question had two aspects "recognition and transition" and "implementation" [of a palliative care approach in advanced heart failure].

8.7.3 Is palliative care effective?

It was shown from the qualitative study that the difficulty appears to be recognition and transition, but if that is successfully negotiated then implementation naturally follows. The effectiveness of the intervention is a separate question and ideally should be evaluated by RCTs such as those described in **section 1.6.1**. However, RCTs where the intervention arm receives specialist palliative care and the comparator does not, will only serve to demonstrate the effectiveness of randomly allocated specialist palliative care. If proven effective, then an expensive and potentially unsustainable service where SPC is provided for all heart failure patients,

will be the logical conclusion with the likely end result that HCPs now providing generalist palliative care will lose these skills entirely.

8.7.4 **Which patients need specialist palliative care?**

These RCTs will not answer the clinically important question of *which* patients would benefit from referral to SPC, and whether management by a heart failure – palliative care integrated team, where patients access services according to need is a more cost-effective approach. Recently, a palliative care needs assessment tool, designed initially designed for use in the oncology clinic, has been adapted for people with heart failure and their carers. The initial validation has been published, but it has yet to be tested in a formal clinical trial[104]. If effective, this assessment tool may be useful in identifying which patients would benefit from specialist referral as well as those who could be managed by the usual care team.

8.7.5 **What is the best way to use initiatives such as GSF?**

Another intervention that would be useful to evaluate is the effectiveness of the GSF in improving patient care and similar outcomes. The GSF has been widely introduced in clinical practice, but has a limited evidence base for effectiveness[234, 322]

8.8 Implications for policy makers

Policy makers, patients and their families share a common goal of avoiding unnecessary hospital admissions in advanced heart failure. The current policy focus on prognosis (last year of life) is unlikely to be successful. The policy was based, among other issues on learning from the successes of palliative care for cancer patients to patients with non-malignant disease. However, recognition of palliative care based on prognosis is not the model of cancer palliative care[234]. An approach based on assessment of need is proposed and would require adequate time and remuneration for the HCP who conducts the assessment[38]. It would need to be appropriately evaluated but it is proposed that this approach (rather than based on prognosis) is more likely to achieve the goal of improving care for patients with life limiting illnesses and reducing unscheduled hospital admissions and health care costs.

8.9 Summary

The aim of this thesis was to explore a palliative care approach for people with advanced heart failure: recognition of need, transitions in care and impact on

patients, family carers and clinicians. The thesis is in response to the challenge laid down by Lingard and colleagues, that is, that researchers of palliative care for patients with heart failure should design and implement research that goes beyond description of the difficulties that patients, carers and clinicians face and the calls for more "communication" to describe practical solutions that can be enacted by the complex team of patient, carers and multiple health care teams[104].

Despite more than a decade of rhetoric regarding a palliative care approach and access to specialist palliative for patients with advanced heart failure the GPRD study has demonstrated a huge inequity in recognition of the need for a palliative care approach for those with heart failure compared with those with cancer. Those with heart failure were not being put on the palliative care register or only in the last weeks of life. A systematic literature review has failed to provide any clinicalmarkers that can be used in daily practice to help with the identification of those who are now in the last year of life. The qualitative study illustrated that patients in this study did want to discuss their life limiting illness and change in focus of care. Clinicians were very concerned about the timing of conversations and delayed until irreversible deterioration was obvious. A variety of factors (including patient initiated) led to a palliative approach to care. All involved found the palliative approach beneficial, even for patients with subsequent periods of stability or improvement. Synthesis of the research findings has led to implications for clinical practice, research and policy. A palliative care approach, available before the "last year of life", would be beneficial for people with heart failure with regard to symptom management, support for patient and carer and assistance with advance care planning. A problem-based flexible approach as the trigger for access to palliative care, rather than one based on prognosis would facilitate this, and should therefore be recommended to policy makers and service providers. Better identification of the "last year of life" may be helpful in clinical practice, especially with regard to advance care planning, but further research is needed. In the meantime, a problem based flexible approach to recognising the need for palliative care, rather than prognosis is recommended.

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10 Appendices

Appendix I Search terms for Ovid Medline

1. exp Heart Failure/

2. exp Ventricular Function/

3. (heart adj failure).mp. [mp=ab, hw, ti, sh, tn, ot, dm, mf, dv, kw, ps, rs, nm, ui]

4. (cardiac adj failure).mp. [mp=ab, hw, ti, sh, tn, ot, dm, mf, dv, kw, ps, rs, nm, ui]

5. (ventricular adj dysfunction).mp. [mp=ab, hw, ti, sh, tn, ot, dm, mf, dv, kw, ps, rs, nm, ui]

6. (ventricular adj systolic adj dysfunction).mp. [mp=ab, hw, ti, sh, tn, ot, dm, mf, dv, kw, ps, rs, nm, ui]

7. (cardiac adj dysfunction).mp. [mp=ab, hw, ti, sh, tn, ot, dm, mf, dv, kw, ps, rs, nm, ui]

8. (cardiac adj function).mp. [mp=ab, hw, ti, sh, tn, ot, dm, mf, dv, kw, ps, rs, nm, ui]

9. (cardiac adj overload).mp. [mp=ab, hw, ti, sh, tn, ot, dm, mf, dv, kw, ps, rs, nm, ui]

10. (systolic adj dysfunction).mp. [mp=ab, hw, ti, sh, tn, ot, dm, mf, dv, kw, ps, rs, nm, ui]

11. (myocard* adj dysfunction).mp. [mp=ab, hw, ti, sh, tn, ot, dm, mf, dv, kw, ps, rs, nm, ui]

12. (cardiac adj insufficiency).mp. [mp=ab, hw, ti, sh, tn, ot, dm, mf, dv, kw, ps, rs, nm, ui]

13. (heart adj insufficiency).mp. [mp=ab, hw, ti, sh, tn, ot, dm, mf, dv, kw, ps, rs, nm, ui]

14. CHF.mp. [mp=ab, hw, ti, sh, tn, ot, dm, mf, dv, kw, ps, rs, nm, ui]

15. CCF.mp. [mp=ab, hw, ti, sh, tn, ot, dm, mf, dv, kw, ps, rs, nm, ui]

16. HF.mp. [mp=ab, hw, ti, sh, tn, ot, dm, mf, dv, kw, ps, rs, nm, ui]

17. LVSD.mp. [mp=ab, hw, ti, sh, tn, ot, dm, mf, dv, kw, ps, rs, nm, ui]

18. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17

19. exp Palliative Care/

20. palliative care.mp. [mp=ab, hw, ti, sh, tn, ot, dm, mf, dv, kw, ps, rs, nm, ui]

21. exp Terminal Care/

22. Terminal Care.mp. [mp=ab, hw, ti, sh, tn, ot, dm, mf, dv, kw, ps, rs, nm, ui]

23. exp Hospice Care/

24. Hospice Care.mp. [mp=ab, hw, ti, sh, tn, ot, dm, mf, dv, kw, ps, rs, nm, ui]

25. (hospice adj care).mp. [mp=ab, hw, ti, sh, tn, ot, dm, mf, dv, kw, ps, rs, nm, ui]

26. (hospice adj caring).mp. [mp=ab, hw, ti, sh, tn, ot, dm, mf, dv, kw, ps, rs, nm, ui]

27. "end stage".mp. [mp=ab, hw, ti, sh, tn, ot, dm, mf, dv, kw, ps, rs, nm, ui]

28. "late stage".mp. [mp=ab, hw, ti, sh, tn, ot, dm, mf, dv, kw, ps, rs, nm, ui]

29. dying.mp. [mp=ab, hw, ti, sh, tn, ot, dm, mf, dv, kw, ps, rs, nm, ui]

30. "end of life".mp. [mp=ab, hw, ti, sh, tn, ot, dm, mf, dv, kw, ps, rs, nm, ui]

31. (terminal* adj ill*).mp. [mp=ab, hw, ti, sh, tn, ot, dm, mf, dv, kw, ps, rs, nm, ui]

32. (advanced adj disease*).mp. [mp=ab, hw, ti, sh, tn, ot, dm, mf, dv, kw, ps, rs, nm, ui]

33. (advanced adj cancer).mp. [mp=ab, hw, ti, sh, tn, ot, dm, mf, dv, kw, ps, rs, nm, ui]

34. (advanced adj illness).mp. [mp=ab, hw, ti, sh, tn, ot, dm, mf, dv, kw, ps, rs, nm, ui]

35. palliat*.mp. [mp=ab, hw, ti, sh, tn, ot, dm, mf, dv, kw, ps, rs, nm, ui]

36. "advance* directive*".mp. [mp=ab, hw, ti, sh, tn, ot, dm, mf, dv, kw, ps, rs, nm, ui]

37. 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36

38. exp Cohort Studies/

39. cohort.mp. [mp=ab, hw, ti, sh, tn, ot, dm, mf, dv, kw, ps, rs, nm, ui]

40. incidence.mp. [mp=ab, hw, ti, sh, tn, ot, dm, mf, dv, kw, ps, rs, nm, ui]

41. exp Mortality/

42. mortality.mp. [mp=ab, hw, ti, sh, tn, ot, dm, mf, dv, kw, ps, rs, nm, ui]

43. follow-up studies.mp. [mp=ab, hw, ti, sh, tn, ot, dm, mf, dv, kw, ps, rs, nm, ui]

44. prognos*.mp. [mp=ab, hw, ti, sh, tn, ot, dm, mf, dv, kw, ps, rs, nm, ui]

45. predict*.mp. [mp=ab, hw, ti, sh, tn, ot, dm, mf, dv, kw, ps, rs, nm, ui]

46. course.mp. [mp=ab, hw, ti, sh, tn, ot, dm, mf, dv, kw, ps, rs, nm, ui]

47. 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46

48. marker*.mp. [mp=ab, hw, ti, sh, tn, ot, dm, mf, dv, kw, ps, rs, nm, ui]

49. Trigger*.mp. [mp=ab, hw, ti, sh, tn, ot, dm, mf, dv, kw, ps, rs, nm, ui]

50. (clinical adj indicator*).mp. [mp=ab, hw, ti, sh, tn, ot, dm, mf, dv, kw, ps, rs, nm, ui]

51. (Estim* adj survival).mp. [mp=ab, hw, ti, sh, tn, ot, dm, mf, dv, kw, ps, rs, nm, ui]

52. Risk score*.mp. [mp=ab, hw, ti, sh, tn, ot, dm, mf, dv, kw, ps, rs, nm, ui]

53. 48 or 49 or 50 or 51 or 52

54. 18 and 37

55. 47 or 53

56. 54 and 55

57. remove duplicates from 26

58. remove duplicates from 34

59. remove duplicates from 17

60. remove duplicates from 9

61. remove duplicates from 15

62. remove duplicates from 51

63. remove duplicates from 13

64. remove duplicates from 6

65. remove duplicates from 50

66. 1 or 2 or 3 or 4 or 5 or 7 or 8 or 10 or 11 or 12 or 14 or 16 or 59 or 60 or 61 or 63 or 64

67. 19 or 20 or 21 or 22 or 23 or 24 or 25 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 35 or 36 or 57 or 58

68. 48 or 49 or 52 or 62 or 65

69. 66 and 67

70. 47 or 68

71. 69 and 70

Appendix 2 Criteria for selecting studies at abstracts stage

Questions being addressed:

Primary research question

What prognostic markers are associated with being in the last year of life in adult patients with heart failure?

Secondary questions

- What groups of prognostic factors best predict outcome? (Outcome prediction)
- What are the interactions between intervention and prognostic factors?

Include abstracts if

- patients have diagnosis of heart failure
- prognostic factors have been investigated

Study types to include

- All randomised or quazi-randomised (blinded and non-blinded) controlled trial including cluster and cross over trials
- Cohort studies (prospective and retrospective)
- Study type unclear

Exclusions

- Only includes paediatric population
- case studies /reviews/opinion pieces

Appendix 3 Criteria for selecting studies at full text stage

Primary research question

What prognostic markers are associated with being in the last year of life in adult patients with heart failure?

Secondary questions

- What groups of prognostic factors best predict outcome? (Outcome prediction)
- What are the interactions between intervention and prognostic factors?

Include article if

- patients have diagnosis of heart failure, but not post-transplant ICD or device insertion.
- prognostic factors have been investigated

Exclude if

- post- transplant , ICD or device insertion
- exclude if specific cause of heart failure such as cardiomyopathy

Study types to include

- All randomised or quazi-randomised (blinded and non-blinded) controlled trial including cluster and cross over trials
- Cohort studies (prospective and retrospective)

Appropriate outcome measure used

- Cardiac death (primary outcome)
- Death from any cause
- Palliative care
- Heart transplant

Exclusions

- Only includes paediatric population
- case studies /reviews/opinion pieces

- Not in English, French, Spanish or Japanese
- Duplicate study, only use data once

FINAL DECISION (PLEASE TICK ONE)

INCLUDE

EXCLUDE, give reason using criteria above

NEEDS DISCUSSION IN RESEARCH GROUP, note points that require discussion overleaf

NEED TO CONTACT AUTHORS TO MAKE DECISION, note points overleaf that require clarification, also think ahead to data extraction phase

Appendix 4 Data extraction tool including risk of bias assessment

- Source
    - Study ID
    - Review author initials
    - Citation and contact details

- Eligibility
    - Confirm eligibility for review
    - Reason for exclusion
- Methods
    - Study design
    - Total study duration
    - Mean follow up
    - NB risk of bias will be assessed separately see next section
- Participants
    - Total number.
    - Setting.
    - Diagnostic criteria for heart failure: echo, clinical etc..
    - Eligibility criteria e.g. NYHA Stage
    - Age.
    - Sex.
    - Country.
- Interventions *if applicable*
    - Total number of intervention groups.

For each intervention and comparison group of interest:

- Specific intervention
- Intervention details

- Prognostic variable/model
    - Name of model and details of each variable

- Outcomes
    - Outcomes and time points (i) collected; (ii) reported

- Outcome definition (with diagnostic criteria if relevant e.g. for cardiac deaths)

- Results
  - Sample size.
  - Missing participants
  - Number of events
  - Statistical model used e.g. cox proportional hazards model
  - Summary data ideally as absolute risk estimates but alternatively as hazard ratio, relative risk ratio or odds ratio

- Miscellaneous
  - Funding source.
  - Key conclusions of the study authors
  - Miscellaneous comments from the study authors
  - References to other relevant studies
  - Correspondence required
  - Miscellaneous comments by the review authors

Risk of bias assessment: Guidelines for Assessing Quality in Prognostic Studies on the Basis of Framework of Potential Biases, taken from Hayden et al, 2006[2]

Table 3. **Guidelines for Assessing Quality in Prognostic Studies on the Basis of Framework of Potential Biases***

Potential Bias	Items To Be Considered for Assessment of Potential Opportunity for Bias
Study participation	
The study sample represents the population of interest on key characteristics, sufficient to limit potential bias to the results. Yes Partly No Unsure	The source population or population of interest is adequately described for key characteristics. The sampling frame and recruitment are adequately described, possibly including methods to identify the sample (number and type used, e.g., referral patterns in health care), period of recruitment, and place of recruitment (setting and geographic location) Inclusion and exclusion criteria are adequately described (e.g., including explicit diagnostic criteria or "zero time" description). There is adequate participation in the study by eligible individuals. The baseline study sample (i.e., individuals entering the study) is adequately described for key characteristics.
Study attrition	
Loss to follow-up (from sample to study population) is not associated with key characteristics (i.e., the study data adequately represent the sample), sufficient to limit potential bias. Yes Partly No Unsure	Response rate (i.e., proportion of study sample completing the study and providing outcome data) is adequate. Attempts to collect information on participants who dropped out of the study are described. Reasons for loss to follow-up are provided. Participants lost to follow-up are adequately described for key characteristics. There are no important differences between key characteristics and outcomes in participants who completed the study and those who did not.
Prognostic factor measurement	
The prognostic factor of interest is adequately measured in study participants to sufficiently limit potential bias. Yes Partly No Unsure	A clear definition or description of the prognostic factor measured is provided (e.g., including dose, level, duration of exposure, and clear specification of the method of measurement). Continuous variables are reported or appropriate (i.e., not data-dependent) cut-points are used. The prognostic factor measure and method are adequately valid and reliable to limit misclassification bias (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and limited reliance on recall). Adequate proportion of the study sample has complete data for prognostic factors. The method and setting of measurement are the same for all study participants. Appropriate methods are used if imputation is used for missing prognostic factor data.
Outcome measurement	
The outcome of interest is adequately measured in study participants to sufficiently limit potential bias. Yes Partly No Unsure	A clear definition of the outcome of interest is provided, including duration of follow-up and level and extent of the outcome construct. The outcome measure and method used are adequately valid and reliable to limit misclassification bias (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and confirmation of outcome with valid and reliable test). The method and setting of measurement are the same for all study participants.
Confounding measurement and account	
Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest. Yes Partly No Unsure	All important confounders, including treatments (key variables in conceptual model), are measured. Clear definitions of the important confounders measured are provided (e.g., including dose, level, and duration of exposures). Measurement of all important confounders is adequately valid and reliable (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and limited reliance on recall). The method and setting of confounding measurement are the same for all study participants. Appropriate methods are used if imputation is used for missing confounder data. Important potential confounders are accounted for in the study design (e.g., matching for key variables, stratification, or initial assembly of comparable groups). Important potential confounders are accounted for in the analysis (i.e., appropriate adjustment).
Analysis	
The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid results. Yes Partly No Unsure	There is sufficient presentation of data to assess the adequacy of the analysis. The strategy for model building (i.e., inclusion of variables) is appropriate and is based on a conceptual framework or model. The selected model is adequate for the design of the study. There is no selective reporting of results.

* Guidelines should be applied on the basis of relevance to the review research question.

[2] Hayden JA, Côté P, Bombardier C. Evaluation of the Quality of Prognosis Studies in Systematic Reviews. *Annals of Internal Medicine* 2006;144(6):427-37.

Appendix 5 List of excluded articles and reason

Excluded because not appropriate type of study: editorial/ review /opinion piece

1. Should dying be a diagnosis? Lancet, 1983. 2 (8344): p. 261.

2. Heart failure beyond maximum medical management. British Journal of Cardiology, 2004. 11 (1): p. 22-23.

3. Abernethy, A.P., PC-FACS: prediction of survival in heart failure. Journal of Palliative Medicine, 2006. 9(4): p. 1021-1022.

4. Acikel, S., et al., Diastolic heart failure in elderly: The prognostic factors and interventions regarding heart failure with preserved ejection fraction. International Journal of Cardiology, 2010. 138 (3): p. 311-313.

5. Balion, C., et al. (2006) Testing for BNP and NT-proBNP in the diagnosis and prognosis of heart failure (Structured abstract). Rockville: Agency for Healthcare Research and Quality (AHRQ) Volume, 437.

6. Belziti, C.A., Prevalence of anemia in heart failure and its effects on prognosis. Expert Review of Cardiovascular Therapy, 2009. 7 (2): p. 131-138.

7. Bernabeu-Wittel, M., et al., Reliability of different criteria in identifying end-of-life trajectory of patients with chronic medical diseases. PALIAR Project. [Spanish]. Revista Espanola de Geriatria y Gerontologia, 2010. 45 (4): p. 203-212.

8. Clerico, A., et al., Clinical relevance of BNP measurement in the follow-up of patients with chronic heart failure. Advances in clinical chemistry, 2009. 48: p. 163-179.

9. Coventry, P.A., et al., Prediction of appropriate timing of palliative care for older adults with non-malignant life-threatening disease: A systematic review. Age and Ageing, 2005. 34 (3): p. 218-227.

10. Edwards, B.S. and R.J. Rodeheffer, Prognostic features in patients with congestive heart failure and selection criteria for cardiac transplantation. Mayo Clinic Proceedings, 1992. 67 (5): p. 485-492.

11. Goldraich, L., L. Beck-da-Silva, and N. Clausell, Are scores useful in advanced heart failure? Expert Review of Cardiovascular Therapy, 2009. 7 (8): p. 985-997.

12. Goldstein, N.E. and D. Fischberg, Update in palliative medicine. Prognosis.

[Commentary on] The Seattle Heart Failure Model: prediction of survival in heart failure. Annals of Internal Medicine, 2008. 148(2): p. 137-138.

13. Goodlin, S.J., T.E. Quill, and R.M. Arnold, Communication and Decision-Making About Prognosis in Heart Failure Care. Journal of Cardiac Failure, 2008. 14 (2): p. 106-113.

14. Hanratty, B., M. Goldacre, and M. Griffith, Making the most of routine data in palliative care research: a case study analysis of linked hospital and mortality data on cancer and heart failure patients in Scotland and Oxford. Palliative Medicine, 2008. 22(6): p. 744-9.

15. Kao, W. and M.R. Costanzo, Prognosis determination in patients with advanced heart failure. Journal of Heart and Lung Transplantation, 1997. 16(6): p. S2-S6.

16. Langberg, M.L. and J.T. Black, Dead souls - Comparing Dartmouth Atlas benchmarks with CMS outcomes data. New England Journal of Medicine, 2009. 361 (22): p. e109.

17. Levy, W.C. and D.T. Linker, Prediction of mortality in patients with heart failure and systolic dysfunction. Current Cardiology Reports, 2008. 10 (3): p. 198-205.

18. Liao, S. and R.M. Arnold, Heart failure and the future of palliative medicine. Journal of Palliative Medicine, 2007. 10(1): p. 184-184.

19. Lietz, K. and L.W. Miller, Patient selection for left-ventricular assist devices. Current Opinion in Cardiology, 2009. 24 (3): p. 246-251.

20. Maisch, B., Is endstage heart disease really terminal? Herz, 1997. 22 (4): p. 181-182.

21. Obialo, C.I., Cardiorenal Consideration as a Risk Factor for Heart Failure. American Journal of Cardiology, 2007. 99 (6 SUPPL. 2): p. S21-S24.

22. Pruszczyk, P., N-terminal pro-brain natriuretic peptide as an indicator of right ventricular dysfunction. Journal of Cardiac Failure, 2005. 11(5): p. S65-S69.

23. Regitz-Zagrosek, V., et al., Sex and gender differences in myocardial hypertrophy and heart failure. Circulation Journal, 2010. 74 (7): p. 1265-1273.

24. Reisfield, G. and G. Wilson, Prognostication in heart failure No.143. J Palliat Med, 2007. 10(1): p. 245-6.

25. Roig, E., [Is anemia a marker of advanced disease or a therapeutic target in heart failure?]. Revista Espanola de Cardiologia, 2005. 58(1): p. 10-2.

26. Rozzini, R., et al., Frailty is a strong modulator of heart failure-associated mortality [2] (multiple letters). Archives of Internal Medicine, 2003. 163 (6): p. 737-738.

27. Stewart, S., Beyond the numbers: The individual challenges of combating consistently poor survival in heart failure. American Heart Journal, 2008. 155 (2): p. 195-196.

28. Strickman, N.E., The pathogenesis and prognosis of end-stage heart disease. Texas Heart Institute Journal, 1987. 14 (4): p. 346-350.

29. Thai, V. and B. Cujec, Transitioning to end-of-life care for patients with advanced heart failure.... Mitchell SL, Teno JM, Kiely DK, Shaffer ML, Jones RN, Prigerson HG, Volicer L, Givens JL, Hamel MB: The clinical course of advanced dementia. N Engl J Med 2009;361:1529-1538. Journal of Palliative Medicine, 2010. 13(7): p. 796-796.

30. Turris, M. and C. Rauscher, Palliative trajectory markers for end-stage heart failure. Or "oh Toto. This doesn't look like kancerous!". Canadian journal of cardiovascular nursing = Journal canadien en soins infirmiers cardio-vasculaires, 2005. 15 (2): p. 17-25.

31. Vranckx, P. and J. Van Cleemput, Prognostic assessment of end-stage cardiac failure. Acta Cardiologica, 1998. 53 (2): p. 121-125.

32. Wada, A., et al., [Prognosis in patients with advanced heart failure]. Nippon Rinsho - Japanese Journal of Clinical Medicine, 2007. 65 Suppl 5: p. 295-9.

33. Workman, S., End-of-life care and congestive heart failure. Archives of Internal Medicine, 2003. 163(6): p. 737.

34. Yusuf, S.W. and J.-B. Durand, Management of heart failure in the elderly. American Journal of Medicine, 2005. 118(12): p. 1446; author reply 1447-8.

Excluded because not investigating prognostic variables

1. Batziou, C., et al., Treatment-induced changes of BNP in patients with end-stage heart failure predict their outcome. Journal of Cardiac Failure, 2006. 12(6): p. S101-S101.

2. Dev, S., et al., Baseline characteristics and outcomes of patients who do not desire resuscitation: An analysis of the ESCAPE trial. Journal of Cardiac Failure, 2009. Conference: 13th Annual Scientific Meeting of the Heart Failure Society of America, HFSA Boston, MA United States. Conference Start: 20090913 Conference End: 20090916. Conference Publication: (var.pagings). 15 (6 SUPPL. 1): p. S91.

3. Felker, G.M., et al. (2009) Biomarker-guided therapy in chronic heart failure: a meta-analysis of randomized controlled trials (Structured abstract). American Heart Journal Volume, 422-430.

4. Funck-Brentano, C., et al. (2000) Predictors of medical events in patients enrolled in the cardiac insufficiency bisoprolol study (CIBIS): a study of the interactions between beta-blocker therapy and occurrence of critical events using analysis of competitive risks. American Heart Journal Volume, 262-71.

5. Gwadry-Sridhar, F.H., et al. (2004) A systematic review and meta-analysis of studies comparing readmission rates and mortality rates in patients with heart failure (Structured abstract). Archives of Internal Medicine Volume, 2315-2320.

6. Healy, D.G., Heart transplant candidates: Factors influencing waiting list mortality. Irish Medical Journal, 2005. 98(10).

7. Jaagosild, P., et al., Outcomes of acute exacerbation of severe congestive heart failure - Quality of life, resource use, and survival. Archives of Internal Medicine, 1998. 158(10): p. 1081-1089.

8. Kao, W.G., et al., ACCEPTANCE TO A CARDIAC TRANSPLANT WAITING LIST IMPROVES PROGNOSIS IN PATIENTS WITH END-STAGE HEART-FAILURE. Clinical Research, 1989. 37(4): p. A881-A881.

9. Levenson, J.W., et al., The last six months of life for patients with congestive heart failure. Journal of the American Geriatrics Society, 2000. 48 (5 SUPPL.): p. S101-S109.

10. Leventhal, M.E., et al. (2011) Swiss Interdisciplinary Management Programme for Heart Failure (SWIM-HF): a randomised controlled trial study of an outpatient inter-professional management programme for heart failure patients in Switzerland. Swiss Medical Weekly Volume, w13171.

11 Lipinski, M.J., et al., Effect of statins and white blood cell count on mortality in patients with ischemic left ventricular dysfunction undergoing percutaneous coronary intervention. Clinical Cardiology, 2006. 29(1): p. 36-41.

12. Mendez, M., et al., Improvement of anaemia is associated with improved survival in elderly heart failure patients. European Journal of Heart Failure, Supplement, 2009. Conference: Heart Failure 2009 Nice France. Conference Start: 20090530 Conference End: 20090602. Conference Publication: (var.pagings). 8: p. ii566-ii567.

13. Miller, W.L., et al., Lower rather than higher levels of B-type natriuretic peptides (NT-pro-BNP and BNP) predict short-term mortality in end-stage heart failure patients treated with nesiritide. American Journal of Cardiology, 2005. 96(6):

p. 837-41.

14. Miller, W.L., et al., Role for precursor Pro-B type natriuretic peptide in assessing response to therapy and prognosis in patients with decompensated heart failure treated with nesiritide. Clinica Chimica Acta, 2009. 406(1-2): p. 119-23.

15. Miller, W.L., et al., Mortality in end stage heart failure is associated with paradoxically low NT-pro BNP and BNP levels: "Natriuretic peptide exhaustion"? Journal of Cardiac Failure, 2004. 10(4): p. S45-S45.

16. Philbin, E.F., et al., Clinical outcomes in heart failure: Report from a community hospital-based registry. American Journal of Medicine, 1999. 107(6): p. 549-555.

17. Stewart, S. and J.D. Horowitz (2002) Home-based intervention in congestive heart failure: long-term implications on readmission and survival. Circulation, 2861-6.

18. Unroe, K.T., et al., Resource use in the last 6 months of life among medicare beneficiaries with heart failure, 2000-2007. Archives of Internal Medicine, 2011. 171 (3): p. 196-203.

Excluded because not appropriate outcome measure ie mortality, palliative care or transplant

1. Ahluwalia, S., et al., Change in Comorbidity Prevalence with Advancing Age Among Persons with Heart Failure. Journal of General Internal Medicine, 2011. 26(10): p. 1145-1151.

2. Al-Khatib, S.M., et al., Incidence and predictors of sudden cardiac death in patients with diastolic heart failure. Journal of Cardiovascular Electrophysiology, 2007. 18(12): p. 1231-1235.

3. Amir, O., et al., Serum oxidative stress level correlates with clinical parameters in chronic systolic heart failure patients. Clinical Cardiology, 2009. 32 (4): p. 199-203.

4. Grady, K.L., et al., Predictors of quality of life in patients with advanced heart failure awaiting transplantation. Journal of Heart and Lung Transplantation, 1995. 14 (11): p. 2-10.

5. Jones, L.G., et al., PREDICTORS OF HOSPICE CARE UTILIZATION BY OLDER ADULTS HOSPITALIZED WITH HEART FAILURE. Gerontologist, 2010. 50: p. 331-331.

6. Levine, T.B., et al., Reversal of end-stage heart failure is predicted by long-

term therapeutic response rather than initial hemodynamic and neurohormonal profile. Journal of Heart and Lung Transplantation, 1996. 15 (3): p. 297-303.

7. Potapov, E.V., et al., Natriuretic peptides as predictors of clinical course in patients with end-stage heart failure. Journal of the American College of Cardiology, 2004. 43(5): p. 170A-171A.

Excluded because not appropriate population as not heart failure patients or clear subgroup of patients with heart failure

1. Arques, S., et al., Comparative value of B-type natriuretic peptide and serum albumin concentration in the prediction of in-hospital mortality in elderly patients admitted for acute severe heart failure. Annales de Cardiologie et d Angeiologie, 2009. 58(5): p. 279-283.

2. Bettencourt, P., et al., Preliminary data on the potential usefulness of B-type natriuretic peptide levels in predicting outcome after hospital discharge in patients with heart failure. American Journal of Medicine, 2002. 113 (3): p. 215-219.

3. Fox, E., et al., Evaluation of prognostic criteria for determining hospice eligibility in patients with advanced lung, heart, or liver disease. Journal of the American Medical Association, 1999. 282 (17): p. 1638-1645.

4. Gustafsson, F., et al., Diagnostic and prognostic performance of N-terminal proBNP in primary care patients with suspected heart failure. Journal of Cardiac Failure, 2005. 11(5): p. S15-20.

5. Hata, N., et al., Acute kidney injury and outcomes in acute decompensated heart failure: Evaluation of the RIFLE criteria in an acutely ill heart failure population. European Journal of Heart Failure, 2010. 12 (1): p. 32-37.

6. Jameson, S., STATISTICAL-DATA SUPPORT PREDICTION OF DEATH WITHIN 6 MONTHS ON LOW-LEVELS OF COENZYME-Q(10) AND OTHER ENTITIES. Clinical Investigator, 1993. 71(8): p. S137-S139.

7. Laudisio, A., et al., Association of left ventricular function with bone mineral density in older women: A population-based study. Calcified Tissue International, 2008. 82 (1): p. 27-33.

8. Lee, J.S.W., et al., Survival prediction in nursing home residents using the Minimum Data Set subscales: ADL Self-Performance Hierarchy, Cognitive Performance and the Changes in Health, End-stage disease and Symptoms and Signs scales. European Journal of Public Health, 2009. 19 (3): p. 308-312.

9. Lynn, J., et al., Prognoses of seriously ill hospitalized patients on the days before death: implications for patient care and public policy. New Horiz, 1997. 5(1):

p. 56-61.

10. Pai, R.G. and P. Varadarajan, Prognostic significance of atrial fibrillation is a function of left ventricular ejection fraction. Clinical Cardiology, 2007. 30 (7): p. 349-354.

11. Porock, D., et al., Predicting death in the nursing home: Development and validation of the 6-month minimum data set mortality risk index. Journals of Gerontology - Series A Biological Sciences and Medical Sciences, 2005. 60 (4): p. 491-498.

12. Schroetter, H., H-FABP in Pre Capillary Pulmonary Hypertension: Comparison to Other Surrogate Parameters for Prediction of Severity and Outcome. Open Journal of Respiratory Diseases, 2011. 01(01): p. 1-13.

13. Silva, T.J.A., et al., Predictors of in-hospital mortality among older patients. Clinics, 2009. 64 (7): p. 613-618.

14. Wright, S.P., et al. (2009) Plasma urocortin 1 in human heart failure. Circulation. Heart failure Volume, 465-71.

Excluded because not appropriate population: post transplant, device or ICD patients

1. Ahmadi-Kashani, M., et al. (2009) Heart rate predicts outcomes in an implantable cardioverter-defibrillator population. Circulation Volume, 2040-5.

2. Beisvag, V., et al., Aetiology-specific patterns in end-stage heart failure patients identified by functional annotation and classification of microarray data. European Journal of Heart Failure, 2006. 8 (4): p. 381-389.

3. Hummel, M., et al., Interleukin-6 and interleukin-8 concentrations as predictors of outcome in ventricular assist device patients before heart transplantation. Critical Care Medicine, 1994. 22 (3): p. 448-454.

4. Liang, H., et al., Prediction of cardiac function after weaning from ventricular assist devices. Journal of Thoracic and Cardiovascular Surgery, 2005. 130 (6): p. 1555-1560.

5. Wei, Y.J., et al., Apolipoprotein D as a novel marker in human end-stage heart failure: A preliminary study. Biomarkers, 2008. 13 (5): p. 535-548.

Excluded because not appropriate type of study asiare case control studies

1. Francis, G.S. and P.J. Boosalis, Mechanism of death in patients with

congestive cardiac failure: the change in plasma norepinephrine and its relation to sudden death. Cardioscience, 1990. 1(1): p. 29-32.

2. Sauvé, M.J., et al., Cognitive impairments in chronic heart failure: a case controlled study. Journal of Cardiac Failure, 2009. 15(1): p. 1-10.

3. Szabo, T., et al., Impaired exercise capacity and metabolic imbalance, the role of adiponectin in progression and symptomatic status of chronic heart failure. European Heart Journal, 2010. Conference: European Society of Cardiology, ESC Congress 2010 Stockholm Sweden. Conference Start: 20100828 Conference End: 20100901. Conference Publication: (var.pagings). 31: p. 933.

Excluded because foreign language (not French, Spanish or Japanese)

1. Duygu, H., et al., Indicators of mortality in patients who are placed on the heart transplant waiting list because of end-stage heart failure. [Turkish]. Turk Kardiyoloji Dernegi Arsivi, 2005. 33 (3): p. 149-154.

2. Duygu, H., et al., Prognostic indicators in patients with end-stage heart failure who are on the waiting list for cardiac transplantation. European Heart Journal, 2005. 26: p. 521-521.

3. Luknar, M., et al., Serum lipoprotein concentration in context of advanced chronic heart failure. [Czech]. Kardiologia, 2005. 14 (6): p. 307-312.

4. Wei, B.Q., et al., Predictive value of admission amino-terminal pro-B-type natriuretic peptide on in-hospital mortality in patients with decompensated heart failure. [Chinese]. Zhonghua xin xue guan bing za zhi [Chinese journal of cardiovascular diseases], 2009. 37 (6): p. 481-485.

5. Wei, B.Q., et al., Value of admission NT-proBNP in predicting in-hospital mortality in decompensated systolic heart failure. [Chinese]. Zhonghua yi xue za zhi, 2009. 89 (28): p. 1955-1959.

6. Xu, D.X., et al., Causes of death analysis in 133 congestive heart failure patients. [Chinese]. Zhonghua xin xue guan bing za zhi [Chinese journal of cardiovascular diseases], 2009. 37 (10): p. 875-877.

Excluded because specific cause of heart failure e.g. cardiomyopathy and so not generalisable

1. Anguita, M., et al., Clinical and hemodynamic predictors of survival in patients aged <65 years with severe congestive heart failure secondary to ischemic or nonischemic dilated cardiomyopathy. American Journal of Cardiology, 1993. 72

(5): p. 413-417.

2. Anguita, M., et al., Are classic predictors of survival of patients with severe congestive heart failure the best? Cardiology Board Review, 1994. 11 (7): p. 23-25+28-29.

3. Caforio, A.L., et al., Elevated serum levels of soluble interleukin-2 receptor, neopterin and beta-2-microglobulin in idiopathic dilated cardiomyopathy: relation to disease severity and autoimmune pathogenesis. European Journal of Heart Failure, 2001. 3(2): p. 155-63.

4. Huang, C.M. and M.S. Young (2002) Long-term survival of non-elderly patients with severe heart failure treated with angiotensin-converting enzyme inhibitors assessment of treatment with captopril and enalapril survival study (ACESS). Circulation journal : official journal of the Japanese Circulation Society Volume, 886-90.

5. Romeo, F., et al., Determinants of end-stage idiopathic dilated cardiomyopathy: A multivariate analysis of 104 patients. Clinical Cardiology, 1989. 12 (7): p. 387-392.

6. Wei, B.Q., J. Zhang, and Y.J. Yang, The value of NT-proBNP at admission in predicting in-hospital mortality in decompensated heart failure due to valvulur heart disease. Cardiology, 2009. Conference: International Heart Forum 2009 Beijing China. Conference Start: 20090911 Conference End: 20090913. Conference Publication: (var.pagings). 114: p. 116-117.

Excluded because conference abstracts and full paper not available

1. Amir, O., et al., Predicting mortality in heart failure patients by echocardiographic parameters; looking beyond the ventricles. European Heart Journal, 2011. Conference: European Society of Cardiology, ESC Congress 2011 Paris France. Conference Start: 20110827 Conference End: 20110831. Conference Publication: (var.pagings). 32: p. 135.

2. Barbandi, M., et al., Echocardiographic predictors of adverse outcome in patients referred for end stage heart failure. Journal of Heart and Lung Transplantation, 2011. Conference: 31st Annual Meeting and Scientific Sessions of the International Society for Heart and Lung Transplantation, ISHLT San Diego, CA United States. Conference Start: 20110413 Conference End: 20110416. Conference Publication: (var.pagings). 30 (4 SUPPL. 1): p. S48.

3. Billia, F., et al., Timely access to care - The seattle heart failure survival score in risk stratification at the time of referral of patients with advanced heart failure:

Dying to be seen. Canadian Journal of Cardiology, 2007. 23: p. 151C-151C.

4. Caccavano, M.H. and C.Y. Jurgens, Palliative care: Missed opportunities for patients with end stage heart failure. Journal of Cardiac Failure, 2010. Conference: 14th Annual Scientific Meeting Heart Failure Society of America San Diego, CA United States. Conference Start: 20100912 Conference End: 20100915. Conference Publication: (var.pagings). 16 (8 SUPPL. 1): p. S104-S105.

5. Canario-Almeida, F., et al., Plasma B-type natriuretic peptide reduction predicts long-term clinical outcome in advanced heart failure patients treated with levosimendan. European Journal of Heart Failure, Supplement, 2009. Conference: Heart Failure 2009 Nice France. Conference Start: 20090530 Conference End: 20090602. Conference Publication: (var.pagings). 8: p. ii451.

6. Gajek, J., et al., Low concentration of ANP in patients in IV NYHA functional class predicts short survival. European Journal of Heart Failure, Supplement, 2009. Conference: Heart Failure 2009 Nice France. Conference Start: 20090530 Conference End: 20090602. Conference Publication: (var.pagings). 8: p. ii129.

7. Iqbal, J., et al., Predictors of outcome in patients with chronic heart failure over a 5 year follow-up period. European Heart Journal, 2011. Conference: European Society of Cardiology, ESC Congress 2011 Paris France. Conference Start: 20110827 Conference End: 20110831. Conference Publication: (var.pagings). 32: p. 284-285.

8. Leong, D., et al., Prediction of outcome for hospitalised heart failure patients: A competing risks analysis. Heart Lung and Circulation, 2010. Conference: New Zealand Annual Scientific Meeting of the Cardiac Society of Australia and New Zealand Adelaide, SA Australia. Conference Start: 20100805 Conference End: 20100808. Conference Publication: (var.pagings). 19: p. S78-S79.

9. Lietz, K., M. Farr, and Y. Naka, Serum albumin concentration as predictor of mortality in patients with end stage heart failure treated medically and with mechanical circulatory support - Analysis of the UNOS/ OPTN data and the DT thoratec registry - Years 1999-2007. Journal of Heart and Lung Transplantation, 2009. Conference: 29th Annual Meeting and Scientific Sessions of the International Society for Heart and Lung Transplantation Paris France. Conference Start: 20090422 Conference End: 20090425. Conference Publication: (var.pagings). 28 (2 SUPPL. 1): p. S173.

10. Mancini, D.M., et al., Predictors of survival in patients with end stage heart failure. Circulation, 2002. 106(19): p. 680-680.

11. Sawa, T., et al., Independent prognostic value of serum albumin in chronic heart failure. Journal of Molecular and Cellular Cardiology, 2010. Conference: 20th World Congress of the International Society for Heart Research Kyoto Japan.

Conference Start: 20100513 Conference End: 20100516. Conference Publication: (var.pagings). 48 (5 SUPPL. 1): p. S119.

12. Schofield, R.S., et al., Clinical outcomes of very elderly patients with acute hospitalization for heart failure. Journal of Cardiac Failure, 2010. Conference: 14th Annual Scientific Meeting Heart Failure Society of America San Diego, CA United States. Conference Start: 20100912 Conference End: 20100915. Conference Publication: (var.pagings). 16 (8 SUPPL. 1): p. S114.

13. Tanada, Y., et al., Independent prognostic value of serum albumin in chronic heart failure. European Journal of Heart Failure, Supplement, 2010. Conference: Heart Failure 2010 Congress Berlin Germany. Conference Start: 20100529 Conference End: 20100601. Conference Publication: (var.pagings). 9: p. S132.

14. Valeur, N., et al., Bilirubin is an independent predictor of mortality in patients with left ventricular systolic dysfunction following acute myocardial infarction. European Heart Journal, 2009. Conference: European Society of Cardiology, ESC Congress 2009 Barcelona Spain. Conference Start: 20090829 Conference End: 20090902. Conference Publication: (var.pagings). 30: p. 874.

15. Whellan, D.J., et al., Referral to hospice and predicted mortality risk among patients hospitalized with heart failure: Findings from GWTG-HF. Journal of the American College of Cardiology, 2011. Conference: 60th Annual Scientific Session of the American College of Cardiology and i2 Summit: Innovation in Intervention, ACC.11 New Orleans, LA United States. Conference Start: 20110402 Conference End: 20110405. Conference Publication: (var.pagings). 57 (14 SUPPL. 1): p. E395.

Excluded because duplicate data, two studies on same group of patients, study that is included in review has longer follow up

1. Brophy, J.M., et al., The hospital course and short term prognosis of patients presenting to the emergency room with decompensated congestive heart failure. Canadian Journal of Cardiology, 1993. 9 (3): p. 219-224.

Excluded as prognostic markers not routinely available in clinical practice

1. AMIR, et al., Circulating Interleukin-10: Association with Higher Mortality in Systolic Heart Failure Patients with Elevated Tumor Necrosis Factor-Alpha. 2010. 12(3): p. 5.

2. Amir, O., et al., Relation between AT1R gene polymorphism and long-term

outcome in patients with heart failure. Cardiology, 2009. 112 (2): p. 151-157.

3. Boisot, S., et al., Serial Sampling of ST2 Predicts 90-Day Mortality Following Destabilized Heart Failure. Journal of Cardiac Failure, 2008. 14 (9): p. 732-738.

4. Chiang, M.C., et al., Vascular cell molecule-1 as a prognostic marker in patients with end-stage heart failure. Acta Cardiologica Sinica, 2004. 20 (2): p. 94-104.

5. de Groote, P., et al., Right ventricular ejection fraction is an independent predictor of survival in patients with moderate heart failure. Journal of the American College of Cardiology, 1998. 32(4): p. 948-954.

6. Doehner, W., S. Von Haehling, and S.D. Anker, Impaired insulin sensitivity in patients with stable chronic heart failure. Cardiology Review, 2006. 23 (4): p. 30-34.

7. Fisher, C., et al. (2003) N-terminal pro B type natriuretic peptide, but not the new putative cardiac hormone relaxin, predicts prognosis in patients with chronic heart failure. Heart (British Cardiac Society) Volume, 879-81.

8. Maestri, R., et al., Prognostic value of non invasive baroreflex sensitivity in chronic heart failure patients, in Computers in Cardiology 2001, Vol 28. 2001, Ieee: New York. p. 597-600.

9. Mejhert, M., et al. (2002) Ventilatory variables are strong prognostic markers in elderly patients with heart failure. Heart (British Cardiac Society) Volume, 239-43.

10. Moore, R.K.G., et al., Heart rate turbulence and death due to cardiac decompensation in patients with chronic heart failure. European Journal of Heart Failure, 2006. 8 (6): p. 585-590.

11. Pan, J.P., et al. (2004) The value of plasma levels of tumor necrosis factor-alpha and interleukin-6 in predicting the severity and prognosis in patients with congestive heart failure. Journal of the Chinese Medical Association : JCMA Volume, 222-8.

12. Rockman, H.A., et al., Long-term predictors of sudden and low output death in chronic congestive heart failure secondary to coronary artery disease. American Journal of Cardiology, 1989. 64 (19): p. 1344-1348.

13. Rosenblum, H., et al., Peak Cardiac Power Measured Noninvasively With a Bioreactance Technique Is a Predictor of Adverse Outcomes in Patients With Advanced Heart Failure. Congestive Heart Failure, 2010. 16 (6): p. 254-258.

14. Røsjø, H., et al. (2010) Prognostic value of chromogranin A in chronic heart failure: data from the GISSI-Heart Failure trial. European Journal of Heart Failure,

549-56.

15. Røysland, R., et al. (2010) Prognostic value of osteoprotegerin in chronic heart failure: The GISSI-HF trial. American Heart Journal, 286-93.

16. Sredniawa, B., et al., Heart rate turbulence for prediction of heart transplantation and mortality in chronic heart failure. Annals of Noninvasive Electrocardiology, 2010. 15 (3): p. 230-237.

17. Stein, P.K. and P. Deedwania (2009) Usefulness of abnormal heart rate turbulence to predict cardiovascular mortality in high-risk patients with acute myocardial infarction and left ventricular dysfunction (from the EPHESUS study). The American journal of cardiology Volume, 1495-9.

18. Stein, P.K., et al., Ambulatory ECG-based T-wave alternans predicts sudden cardiac death in high-risk post-MI patients with left ventricular dysfunction in the EPHESUS study. Journal of Cardiovascular Electrophysiology, 2008. 19 (10): p. 1037-1042.

19. White, M., et al., Decreased coronary sinus oxygen content: A predictor of adverse prognosis in patients with severe congestive heart failure. Journal of the American College of Cardiology, 1991. 18 (7): p. 1631-1637.

Excluded as papers with higher risk of bias, Haden score ≤ 8

Aaronson, K.D., et al., Development and prospective validation of a clinical index to predict survival in ambulatory patients referred for cardiac transplant evaluation. Circulation, 1997. 95 (12): p. 2660-2667.

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Appendix 6 Differences between protocol and review

Methods

Types of participants

Inclusion criteria

All patients over 18 years with a diagnosis of heart failure **added including with 'preserved' ejection fraction (diastolic heart failure).**

The reason for this addition is that heart failure with "preserved EF" is increasingly recognised (see **section 1.4**). Unfortunately, many of the studies did not make it clear if they were including patients with diastolic heart failure or not. It has implications, for example if using EF as a prognostic marker and using normal EF as a reference range.

Exclusion criteria

Added **populations where all participants had one specific cause of heart failure e.g. a cardiomyopathy, post-transplant or all had ICD or other device** as these populations are not generalisable

Types of outcome measures

Primary

Death from any cause (changed from secondary outcome) as the Cox multiple regression (the data of interest) was most commonly carried out on all-cause mortality, and rarely on other outcomes. It is also more accurately measured than other outcomes such as cardiac death.

Secondary

Cardiac death (**changed from primary outcome**)

Transition to palliative care approach

Heart transplant

Additional criteria were added

Other criteria

Inclusion

Only studies that were at a low risk of bias were included. An arbitrary score was added to the Hayden risk of bias tool with yes =2, partly =1, no or unclear =0 with a possible score of between 0 to 12. All texts with a score greater than or equal to 9 were included in the final review.

Exclusion

Studies that investigated prognostic markers that are not routinely available in clinical practice were excluded.

Search strategy

However this may miss some general non-disease specific markers of the last year of life and so will also search for palliative care and (prognostic studies and markers). **When this search strategy was tried the number of hits were too numerous to allow searching and so was not done**.

Did not contact experts in the field, especially for unpublished data, as there were no clear expert groups to contact and no evidence of unpublished data. A pragmatic decision was made to exclude conference abstracts when no full text articles were available.

Data extraction plans

Data from the included studies were added to a data extract form by a single reviewer, instead of two reviewers. Again this was a pragmatic decision based on the number of papers that needed to be reviewed.

Validity assessment/ risk of bias assessment

It was planned to use sensitivity analysis to exclude studies at high risk of bias (e.g. scoring at high risk on more than 4 of the domains) from the analysis and examine the effects this has on the results. However, as excluded all studies at high risk of bias this was not possible.

Data analysis plans

Meta-analysis was not possible for the reasons described in the main text. The protocol plan for meta-analysis is outlined below.

For each outcome, we plan to combine estimates of the hazard ratio, odds ratio, or relative risk from studies using the "meta" command of Stata, version 11.0 This command also tests for the presence of heterogeneity.13 There is likely to be significant clinical and statistical heterogeneity so formal meta-analysis may not be possible.

If meta-analysis is possible, statistical heterogeneity will be tested using a Chi-squared test and visual inspection of graphs. A significance level of less than 0.10 would be set as evidence of heterogeneity. I2 would also be calculated as an index of heterogenetity. For interpreting I2= 0% no heterogeneity, I2 = 25% low heterogeneity, I2= 50% moderate heterogeneity, I2= 75% high heterogeneity.14 A fixed-effects model will be used. If significant statistical heterogeneity data would be

reanalysed using a random-effects model. If heterogeneity is identified subgroup analysis will be undertaken to explore the lack of homogeneity.

The final planned analysis is to investigate whether the review was subject to publication bias by visual examination of a funnel plot for signs of asymmetry. However, funnel plots have limited power to detect bias if the number of studies is small.

Appendix 7 Table of medcodes for GPRD

medcode	readcode	readterm
318	B210.00	Malignant neoplasm of glottis
319	B21..00	Malignant neoplasm of larynx
348	B34..11	Ca female breast
779	B49..00	Malignant neoplasm of urinary bladder
780	B46..00	Malignant neoplasm of prostate
782	B....00	Neoplasms
865	B32..00	Malignant melanoma of skin
1056	B5z..00	Malignant neoplasm of other and unspecified site NOS
1062	B10..00	Malignant neoplasm of oesophagus
1220	B13..00	Malignant neoplasm of colon
1481	B600.00	Reticulosarcoma
1599	B4A0.00	Malignant neoplasm of kidney parenchyma
1800	B141.00	Malignant neoplasm of rectum
1952	B580.00	Secondary malignant neoplasm of kidney
1986	B440.11	Cancer of ovary
2462	B61..00	Hodgkin's disease
2587	B22z.11	Lung cancer
2744	B40..00	Malignant neoplasm of uterus, part unspecified
2747	B41..00	Malignant neoplasm of cervix uteri
2755	B....11	Cancers
2815	B133.00	Malignant neoplasm of sigmoid colon
2890	B430200	Malignant neoplasm of endometrium of corpus uteri
2961	B47z.11	Seminoma of testis
3213	B430.00	Malignant neoplasm of corpus uteri, excluding isthmus
3230	B41..11	Cervical carcinoma (uterus)
3357	B1...11	Carcinoma of digestive organs and peritoneum
3541	B48..00	Malignant neoplasm of penis and other male genital organs

3604	B627.00	Non - Hodgkin's lymphoma
3811	B134.00	Malignant neoplasm of caecum
3903	B22z.00	Malignant neoplasm of bronchus or lung NOS
3968	B34..00	Malignant neoplasm of female breast
4072	B680.00	Acute leukaemia NOS
4137	B570.00	Secondary malignant neoplasm of lung
4218	B541.00	Malignant neoplasm of parathyroid gland
4222	B64..11	Lymphatic leukaemia
4250	B68z.00	Leukaemia NOS
4251	B640.00	Acute lymphoid leukaemia
4388	B020.00	Malignant neoplasm of parotid gland
4403	B577.11	Liver metastases
4413	B650.00	Acute myeloid leukaemia
4554	B454.00	Malignant neoplasm of vulva unspecified
4555	B45..00	Malig neop of other and unspecified female genital organs
4865	B10z.11	Oesophageal cancer
4870	B625.11	Histiocytosis X (acute, progressive)
4944	B630.00	Multiple myeloma
5062	B30..11	Chondroma
5137	B624.11	Leukaemic reticuloendotheliosis
5179	B620.00	Nodular lymphoma (Brill - Symmers disease)
5198	B583000	Secondary malignant neoplasm of brain
5199	B583200	Cerebral metastasis
5637	B53..00	Malignant neoplasm of thyroid gland
5842	B58..00	Secondary malignant neoplasm of other specified sites
5901	B141.12	Rectal carcinoma
6115	B6y0.00	Myeloproliferative disorder
6170	B590.11	Carcinomatosis
6471	B57..11	Metastases of respiratory and/or digestive systems

6701	B565.00	Secondary and unspec malig neop intrapelvic lymph nodes
6806	B12..00	Malignant neoplasm of small intestine and duodenum
6935	B131.00	Malignant neoplasm of transverse colon
7046	B43..00	Malignant neoplasm of body of uterus
7176	B65..00	Myeloid leukaemia
7219	B141.11	Carcinoma of rectum
7484	B226.00	Mesothelioma
7654	B585.00	Secondary malignant neoplasm of bone and bone marrow
7740	B470200	Seminoma of undescended testis
7805	B440.00	Malignant neoplasm of ovary
7830	B56..11	Lymph node metastases
7940	ByuDF11	[X]Non-Hodgkin's lymphoma NOS
7978	B4A0000	Hypernephroma
7982	B161200	Malignant neoplasm of common bile duct
8154	B576200	Malignant ascites
8166	B17..00	Malignant neoplasm of pancreas
8386	B11..00	Malignant neoplasm of stomach
8550	B542000	Malignant neoplasm of pituitary gland
8625	B641.00	Chronic lymphoid leukaemia
8649	ByuDF00	[X]Non-Hodgkin's lymphoma, unspecified type
8693	B5...11	Carcinoma of other and unspecified sites
8771	B170.00	Malignant neoplasm of head of pancreas
8918	B15..00	Malignant neoplasm of liver and intrahepatic bile ducts
9030	B55..00	Malignant neoplasm of other and ill-defined sites
9088	B130.00	Malignant neoplasm of hepatic flexure of colon
9118	B13z.11	Colonic cancer
9237	B21z.00	Malignant neoplasm of larynx NOS
9470	B34z.00	Malignant neoplasm of female breast NOS
9476	B471100	Teratoma of descended testis

9491	B142.11	Anal carcinoma
9505	B582600	Secondary malignant neoplasm of skin of breast
9600	B232.00	Mesothelioma of pleura
9618	B56..00	Secondary and unspecified malignant neoplasm of lymph nodes
9622	B525.00	Malignant neoplasm of cauda equina
9902	B3...11	Carcinoma of bone, connective tissue, skin and breast
9984	B00..11	Carcinoma of lip
10283	B01..00	Malignant neoplasm of tongue
10314	B057.00	Overlapping lesion of other and unspecified parts of mouth
10358	B222.00	Malignant neoplasm of upper lobe, bronchus or lung
10368	B11..11	Gastric neoplasm
10698	B450100	Malignant neoplasm of vaginal vault
10726	B651.00	Chronic myeloid leukaemia
10851	B51..11	Cerebral tumour - malignant
10864	B132.00	Malignant neoplasm of descending colon
10946	B136.00	Malignant neoplasm of ascending colon
10949	B162.00	Malignant neoplasm of ampulla of Vater
10995	B5...00	Malignant neoplasm of other and unspecified sites
11009	B1z..00	Malig neop oth/ill-defined sites digestive tract/peritoneum
11035	B593.00	Primary malignant neoplasm of unknown site
11628	B1z0.11	Cancer of bowel
11991	B454.11	Primary vulval cancer
12006	B621.00	Mycosis fungoides
12323	B6...00	Malignant neoplasm of lymphatic and haemopoietic tissue
12335	B62y.00	Malignant lymphoma NOS
12389	B4A1.00	Malignant neoplasm of renal pelvis
12464	B62x200	Peripheral T-cell lymphoma
12490	B550200	Malignant neoplasm of nose NOS
12499	Byu6.00	[X]Malignant neoplasm of breast

12539	B3...12	Sarcoma of bone and connective tissue
12582	B224100	Malignant neoplasm of lower lobe of lung
12870	B221.00	Malignant neoplasm of main bronchus
13243	B22..00	Malignant neoplasm of trachea, bronchus and lung
13252	B4...00	Malignant neoplasm of genitourinary organ
13559	B4A..00	Malig neop of kidney and other unspecified urinary organs
13569	B590.00	Disseminated malignancy NOS
14712	B00..00	Malignant neoplasm of lip
14792	B05..00	Malignant neoplasm of other and unspecified parts of mouth
14800	B11z.00	Malignant neoplasm of stomach NOS
15027	B62yz00	Malignant lymphoma NOS
15036	B626.00	Malignant mast cell tumours
15103	B577.00	Secondary malignant neoplasm of liver
15148	B47..00	Malignant neoplasm of testis
15182	B31z.00	Malignant neoplasm of connective and soft tissue, site NOS
15211	B630.12	Myelomatosis
15221	B220.00	Malignant neoplasm of trachea
15223	B4A2.00	Malignant neoplasm of ureter
15504	B62y800	Malignant lymphoma NOS of lymph nodes of multiple sites
15507	B56z.00	Secondary and unspec malig neop lymph nodes NOS
15644	B4A3.00	Malignant neoplasm of urethra
15684	B204.00	Malignant neoplasm of frontal sinus
15709	B1...00	Malignant neoplasm of digestive organs and peritoneum
15711	B510.00	Malignant neoplasm cerebrum (excluding lobes and ventricles)
15907	B16z.00	Malignant neoplasm gallbladder/extrahepatic bile ducts NOS
15976	B552.00	Malignant neoplasm of abdomen
15989	B47z.12	Teratoma of testis
15991	B506.00	Malignant neoplasm of choroid
16075	B30z.00	Malignant neoplasm of bone and articular cartilage NOS

16105	B160.00	Malignant neoplasm of gallbladder
16126	B150000	Primary carcinoma of liver
16213	B572.00	Secondary malignant neoplasm of pleura
16241	B060.00	Malignant neoplasm of tonsil
16280	B550400	Malignant neoplasm of neck NOS
16297	B0z0.00	Malignant neoplasm of pharynx unspecified
16298	B18z.00	Malignant neoplasm of retroperitoneum and peritoneum NOS
16416	B681.00	Chronic leukaemia NOS
16500	B58z.00	Secondary malignant neoplasm of other specified site NOS
16704	B302.00	Malignant neoplasm of vertebral column
16760	B58y000	Secondary malignant neoplasm of breast
16874	B4...11	Carcinoma of genitourinary organ
16915	B151.00	Malignant neoplasm of intrahepatic bile ducts
16967	B432.00	Malignant neoplasm of overlapping lesion of corpus uteri
17056	B6y0.11	Myeloproliferative disease
17182	B627C11	Follicular lymphoma NOS
17391	B221000	Malignant neoplasm of carina of bronchus
17460	B627700	Diffuse non-Hodgkin's lymphoblastic (diffuse) lymphoma
17475	B300A00	Malignant neoplasm of maxilla
17559	B1z0.00	Malignant neoplasm of intestinal tract, part unspecified
17841	B481.00	Malignant neoplasm of glans penis
17874	B181.00	Mesothelioma of peritoneum
17887	B62x.00	Malignant lymphoma otherwise specified
17912	B042.00	Malignant neoplasm, overlapping lesion of floor of mouth
18231	B540.11	Phaeochromocytoma
18314	B30..00	Malignant neoplasm of bone and articular cartilage
18608	B3...00	Malig neop of bone, connective tissue, skin and breast
18613	B120.00	Malignant neoplasm of duodenum
18616	B58y.00	Secondary malignant neoplasm of other specified sites

18617	B51..00	Malignant neoplasm of brain
18619	B137.00	Malignant neoplasm of splenic flexure of colon
18632	B135.00	Malignant neoplasm of appendix
18658	B562300	Secondary and unspec malig neop common iliac lymph nodes
18676	B585000	Pathological fracture due to metastatic bone disease
18678	B224000	Malignant neoplasm of lower lobe bronchus
18712	B4A..11	Renal malignant neoplasm
18882	B006.00	Malignant neoplasm of overlapping lesion of lip
19028	B630100	Solitary myeloma
19140	B614800	Hodgkin's nodular sclerosis of lymph nodes of multiple sites
19141	B44..00	Malignant neoplasm of ovary and other uterine adnexa
19144	Byu4.00	[X]Melanoma and other malignant neoplasms of skin
19162	B493.00	Malignant neoplasm of anterior wall of urinary bladder
19226	B513.00	Malignant neoplasm of parietal lobe
19318	B112.00	Malignant neoplasm of pyloric antrum of stomach
19321	B311300	Malignant neoplasm of connective and soft tissue of hand
19372	B64..00	Lymphoid leukaemia
19389	B3y..00	Malig neop of bone, connective tissue, skin and breast OS
19415	B0...00	Malignant neoplasm of lip, oral cavity and pharynx
19423	B35..00	Malignant neoplasm of male breast
19437	B30z000	Osteosarcoma
19444	Byu4100	[X]Malignant melanoma of skin, unspecified
19475	B471.00	Malignant neoplasm of descended testis
19945	B582.00	Secondary malignant neoplasm of skin
19974	B660.00	Acute monocytic leukaemia
20092	B04..00	Malignant neoplasm of floor of mouth
20159	B56y.00	Secondary and unspec malig neop lymph nodes multiple sites
20160	B50..00	Malignant neoplasm of eye
20166	B45z.00	Malignant neoplasm of female genital organ NOS

20170	B222.11	Pancoast's syndrome
20292	B02..00	Malignant neoplasm of major salivary glands
20440	B69..00	Myelomonocytic leukaemia
20685	B346.00	Malignant neoplasm of axillary tail of female breast
21329	B630200	Plasmacytoma NOS
21330	B180.00	Malignant neoplasm of retroperitoneum
21402	B602.00	Burkitt's lymphoma
21549	B627C00	Follicular non-Hodgkin's lymphoma
21590	B58y500	Secondary malignant neoplasm of prostate
21620	B111.00	Malignant neoplasm of pylorus of stomach
21698	B221z00	Malignant neoplasm of main bronchus NOS
21715	Byu5011	[X]Mesothelioma of lung
21786	B471000	Seminoma of descended testis
22050	B691.00	Chronic myelomonocytic leukaemia
22146	B581100	Secondary malignant neoplasm of bladder
22158	B630000	Malignant plasma cell neoplasm, extramedullary plasmacytoma
22163	B134.11	Carcinoma of caecum
22187	B150300	Hepatocellular carcinoma
22290	B313.00	Malignant neoplasm of connective and soft tissue of thorax
22441	B212.00	Malignant neoplasm of subglottis
22524	B58yz00	Secondary malignant neoplasm of other specified site NOS
22893	B06..00	Malignant neoplasm of oropharynx
22894	B110100	Malignant neoplasm of cardio-oesophageal junction of stomach
23380	B340000	Malignant neoplasm of nipple of female breast
23389	B200.00	Malignant neoplasm of nasal cavities
23399	B344.00	Malignant neoplasm of upper-outer quadrant of female breast
23433	B161.00	Malignant neoplasm of extrahepatic bile ducts
23861	B551100	Malignant neoplasm of chest wall NOS
24048	B180200	Malignant neoplasm of retrocaecal tissue

24235	B524.00	Malig neopl peripheral nerves and autonomic nervous system
24301	B57..12	Secondary carcinoma of respiratory and/or digestive systems
24370	B142.00	Malignant neoplasm of anal canal
24374	B0...11	Carcinoma of lip, oral cavity and pharynx
24397	B061.00	Malignant neoplasm of tonsillar fossa
24456	B201.00	Malig neop auditory tube, middle ear and mastoid air cells
24675	B07..00	Malignant neoplasm of nasopharynx
24852	B016.00	Malignant neoplasm of lingual tonsil
25191	B68..00	Leukaemia of unspecified cell type
25366	B561300	Secondary and unspec malig neop ant mediastinal lymph nodes
25535	B150.00	Primary malignant neoplasm of liver
25602	B326400	Malignant melanoma of finger
25886	B222100	Malignant neoplasm of upper lobe of lung
26034	B591.00	Other malignant neoplasm NOS
26134	B064000	Malignant neoplasm of epiglottis, free border
26165	B211.00	Malignant neoplasm of supraglottis
26393	B152.00	Malignant neoplasm of liver unspecified
26448	B060000	Malignant neoplasm of faucial tonsil
26454	B45X.00	Malignant neoplasm/overlapping lesion/feml genital organs
26652	B20..00	Malig neop nasal cavities, middle ear and accessory sinuses
26813	B21y.00	Malignant neoplasm of larynx, other specified site
26853	B340.00	Malignant neoplasm of nipple and areola of female breast
27330	B624.00	Leukaemic reticuloendotheliosis
27340	B670.11	Di Guglielmo's disease
27391	B576100	Secondary malignant neoplasm of peritoneum
27416	B601.00	Lymphosarcoma
27449	B554.00	Malignant neoplasm of upper limb NOS
27458	B661.00	Chronic monocytic leukaemia
27483	B240.00	Malignant neoplasm of thymus

27520	B651z00	Chronic myeloid leukaemia NOS
27528	B303.00	Malignant neoplasm of ribs, sternum and clavicle
27540	B4A1000	Malignant neoplasm of renal calyces
27617	B45y000	Malignant neoplasm of overlapping lesion of vulva
27651	B58..11	Secondary carcinoma of other specified sites
27664	B65y100	Acute promyelocytic leukaemia
27715	B242.00	Malignant neoplasm of anterior mediastinum
27790	B641.11	Chronic lymphatic leukaemia
27855	B140.00	Malignant neoplasm of rectosigmoid junction
27897	B143.00	Malignant neoplasm of anus unspecified
28003	B420.00	Choriocarcinoma
28059	B560600	Secondary and unspec malig neop of facial lymph nodes
28069	B505.00	Malignant neoplasm of retina
28148	B540.00	Malignant neoplasm of adrenal gland
28163	B13z.00	Malignant neoplasm of colon NOS
28241	B496.00	Malignant neoplasm of ureteric orifice
28276	B675.00	Acute myelofibrosis
28311	B41z.00	Malignant neoplasm of cervix uteri NOS
28451	B08z.00	Malignant neoplasm of hypopharynx NOS
28556	B32z.00	Malignant melanoma of skin NOS
28559	B055z00	Malignant neoplasm of palate NOS
28639	B627000	Follicular non-Hodgkin's small cleaved cell lymphoma
28665	B07z.00	Malignant neoplasm of nasopharynx NOS
28727	B575000	Secondary malignant neoplasm of colon
28919	B521.00	Malignant neoplasm of cerebral meninges
29160	B313000	Malignant neoplasm of connective and soft tissue of axilla
29178	B614.00	Hodgkin's disease, nodular sclerosis
29283	B2zy.00	Malignant neoplasm of other site of respiratory tract
29462	B4Az.00	Malignant neoplasm of kidney or urinary organs NOS

29735	B30..12	Osteoma
29826	B342.00	Malignant neoplasm of upper-inner quadrant of female breast
29876	B613z00	Hodgkin's, lymphocytic-histiocytic predominance NOS
30165	B18y200	Malignant neoplasm of mesorectum
30402	B050.11	Malignant neoplasm of buccal mucosa
30511	B54..00	Malig neop of other endocrine glands and related structures
30526	Byu5100	[X]Mesothelioma, unspecified
30542	B312300	Malig neop of connective and soft tissue of lower leg
30632	B67z.00	Other specified leukaemia NOS
30646	B6y..00	Malignant neoplasm lymphatic or haematopoietic tissue OS
30700	B10z.00	Malignant neoplasm of oesophagus NOS
31102	B49z.00	Malignant neoplasm of urinary bladder NOS
31188	B224.00	Malignant neoplasm of lower lobe, bronchus or lung
31210	B150100	Hepatoblastoma of liver
31268	B223.00	Malignant neoplasm of middle lobe, bronchus or lung
31324	B626800	Mast cell malignancy of lymph nodes of multiple sites
31364	B050.00	Malignant neoplasm of cheek mucosa
31393	B160.11	Carcinoma gallbladder
31399	B555.00	Malignant neoplasm of lower limb NOS
31546	B341.00	Malignant neoplasm of central part of female breast
31573	B23..00	Malignant neoplasm of pleura
31576	B627B00	Other types of follicular non-Hodgkin's lymphoma
31586	B64y100	Prolymphocytic leukaemia
31608	B43y.00	Malignant neoplasm of other site of uterine body
31700	B222000	Malignant neoplasm of upper lobe bronchus
31701	B651.11	Chronic granulocytic leukaemia
31794	B627W00	Unspecified B-cell non-Hodgkin's lymphoma
32022	B110.00	Malignant neoplasm of cardia of stomach
32024	B030.00	Malignant neoplasm of upper gum

32174	B202.00	Malignant neoplasm of maxillary sinus
32362	B113.00	Malignant neoplasm of fundus of stomach
32372	B302100	Malignant neoplasm of thoracic vertebra
32768	B325100	Malignant melanoma of breast
32955	B41y.00	Malignant neoplasm of other site of cervix
33333	B62..00	Other malignant neoplasm of lymphoid and histiocytic tissue
33344	B65z.00	Myeloid leukaemia NOS
33388	B071000	Malignant neoplasm of adenoid
33395	B560200	Secondary and unspec malig neop superficial cervical LN
33444	B221100	Malignant neoplasm of hilus of lung
33617	B43z.00	Malignant neoplasm of body of uterus NOS
33833	B301.00	Malignant neoplasm of mandible
33843	B583.00	Secondary malignant neoplasm of brain and spinal cord
33871	B122.00	Malignant neoplasm of ileum
34012	B08..00	Malignant neoplasm of hypopharynx
34075	B2...00	Malig neop of respiratory tract and intrathoracic organs
34089	B62y400	Malignant lymphoma NOS of lymph nodes of axilla and arm
34145	B58y600	Secondary malignant neoplasm of testis
34259	B325300	Malignant melanoma of groin
34388	B17z.00	Malignant neoplasm of pancreas NOS
34409	B010000	Malignant neoplasm of base of tongue dorsal surface
34451	B31..00	Malignant neoplasm of connective and other soft tissue
34692	B68y.00	Other leukaemia of unspecified cell type
34742	B23z.00	Malignant neoplasm of pleura NOS
34878	B308300	Malignant neoplasm of medial cuneiform
34926	B625.00	Letterer-Siwe disease
35014	B622.00	Sezary's disease
35039	B163.00	Malignant neoplasm, overlapping lesion of biliary tract
35053	B57..00	Secondary malig neop of respiratory and digestive systems

35113	Byu9.00	[X]Malignant neoplasm of urinary tract
35180	Byu1.00	[X]Malignant neoplasm of digestive organs
35186	ByuC.00	[X]Malignant neoplasm of ill-defined, secondary and unspeci
35285	ByuA.00	[X]Malignant neoplasm of eye, brain and other parts of cent
35325	Byu2.00	[X]Malignant neoplasm of respiratory and intrathoracic orga
35357	B14..00	Malignant neoplasm of rectum, rectosigmoid junction and anus
35364	B576000	Secondary malignant neoplasm of retroperitoneum
35535	B173.00	Malignant neoplasm of pancreatic duct
35795	B174.00	Malignant neoplasm of Islets of Langerhans
35875	B66..00	Monocytic leukaemia
35963	B492.00	Malignant neoplasm of lateral wall of urinary bladder
35999	B582200	Secondary malignant neoplasm of skin of neck
36147	B153.00	Secondary malignant neoplasm of liver
36161	B012.00	Malignant neoplasm of tongue, tip and lateral border
36200	B575z00	Secondary malig neop of large intestine or rectum NOS
36325	B470300	Teratoma of undescended testis
36371	B225.00	Malignant neoplasm of overlapping lesion of bronchus & lung
36401	B587.00	Secondary malignant neoplasm of adrenal gland
36495	B161211	Carcinoma common bile duct
36716	B04z.00	Malignant neoplasm of floor of mouth NOS
36899	B327800	Malignant melanoma of toe
36949	B49y.00	Malignant neoplasm of other site of urinary bladder
37096	B015.00	Malignant neoplasm of tongue, junctional zone
37112	B6...11	Malignant neoplasm of histiocytic tissue
37182	B63..00	Multiple myeloma and immunoproliferative neoplasms
37272	B67..00	Other specified leukaemia
37328	B450.00	Malignant neoplasm of vagina
37461	B64y200	Adult T-cell leukaemia
37468	B671.00	Chronic erythraemia

37516	B054.00	Malignant neoplasm of uvula
37540	B563000	Secondary and unspec malig neop axillary lymph nodes
37549	B05z000	Kaposi's sarcoma of palate
37553	B007.00	Malignant neoplasm of lip, unspecified
37590	B052.00	Malignant neoplasm of hard palate
37618	B551000	Malignant neoplasm of axilla NOS
37724	B056.00	Malignant neoplasm of retromolar area
37805	B213100	Malignant neoplasm of cricoid cartilage
37810	B220z00	Malignant neoplasm of trachea NOS
37842	B303000	Malignant neoplasm of rib
37859	B110z00	Malignant neoplasm of cardia of stomach NOS
37872	B327400	Malignant melanoma of lower leg
37916	B05y.00	Malignant neoplasm of other specified mouth parts
37919	B561000	Secondary and unspec malig neop internal mammary lymph nodes
37940	B072000	Malignant neoplasm of pharyngeal recess
38005	B621z00	Mycosis fungoides NOS
38331	B64yz00	Other lymphoid leukaemia NOS
38343	B560700	Secondary and unspec malig neop submental lymph nodes
38475	B34yz00	Malignant neoplasm of other site of female breast NOS
38488	B013z00	Malignant neoplasm of ventral tongue surface NOS
38510	B47z.00	Malignant neoplasm of testis NOS
38689	B325.00	Malignant melanoma of trunk (excluding scrotum)
38736	B5y..00	Malignant neoplasm of other and unspecified site OS
38862	B490.00	Malignant neoplasm of trigone of urinary bladder
38914	B64z.00	Lymphoid leukaemia NOS
38918	B583100	Secondary malignant neoplasm of spinal cord
38931	B4y..00	Malignant neoplasm of genitourinary organ OS
38938	B306z00	Malignant neoplasm of pelvis, sacrum or coccyx NOS
38939	B613.00	Hodgkin's disease, lymphocytic-histiocytic predominance

38961	B22y.00	Malignant neoplasm of other sites of bronchus or lung
38978	B15z.00	Malignant neoplasm of liver and intrahepatic bile ducts NOS
39027	ByuC000	[X]Malignant neoplasm of other specified sites
39084	B0z2.00	Malignant neoplasm of laryngopharynx
39088	B514.00	Malignant neoplasm of occipital lobe
39187	B631.00	Plasma cell leukaemia
39336	B6y1.00	Myelosclerosis with myeloid metaplasia
39413	B18y500	Malignant neoplasm of pelvic peritoneum
39430	B0zz.00	Malignant neoplasm of lip, oral cavity and pharynx NOS
39433	B560500	Secondary and unspec malig neop submandibular lymph nodes
39531	B25..00	Malig neo, overlapping lesion of heart, mediastinum & pleura
39554	B063.00	Malignant neoplasm of vallecula
39590	B206.00	Malignant neoplasm, overlapping lesion of accessory sinuses
39629	B653100	Granulocytic sarcoma
39798	B627X00	Diffuse non-Hodgkin's lymphoma, unspecified
39870	B172.00	Malignant neoplasm of tail of pancreas
39878	B327300	Malignant melanoma of popliteal fossa area
39897	B081.00	Malignant neoplasm of pyriform sinus
39899	B542100	Malignant neoplasm of craniopharyngeal duct
39923	B223100	Malignant neoplasm of middle lobe of lung
40014	B310100	Malignant neoplasm of soft tissue of face
40292	B053.00	Malignant neoplasm of soft palate
40437	B50y.00	Malignant neoplasm of other specified site of eye
40557	B01z.00	Malignant neoplasm of tongue NOS
40592	Byu5.00	[X]Malignant neoplasm of mesothelial and soft tissue
40595	Byu2000	[X]Malignant neoplasm of bronchus or lung, unspecified
40598	Byu7.00	[X]Malignant neoplasm of female genital organs
40608	ByuB.00	[X]Malignant neoplasm of thyroid and other endocrine glands
40671	Byu8.00	[X]Malignant neoplasm of male genital organs

40740	ByuD.00	[X]Malignant neoplasms of lymphoid, haematopoietic and rela
40749	Byu3.00	[X]Malignant neoplasm of bone and articular cartilage
40810	B171.00	Malignant neoplasm of body of pancreas
40814	B307200	Malignant neoplasm of tibia
40966	B306300	Malignant neoplasm of sacral vertebra
41011	B3z..00	Malig neop of bone, connective tissue, skin and breast NOS
41144	B582300	Secondary malignant neoplasm of skin of trunk
41215	B111100	Malignant neoplasm of pyloric canal of stomach
41278	B323000	Malignant melanoma of external surface of cheek
41362	B101.00	Malignant neoplasm of thoracic oesophagus
41369	B60..00	Lymphosarcoma and reticulosarcoma
41490	B327700	Malignant melanoma of foot
41515	ByuA100	[X]Malignant neoplasm/central nervous system, unspecified
41520	B51z.00	Malignant neoplasm of brain NOS
41523	B223000	Malignant neoplasm of middle lobe bronchus
41530	B01y.00	Malignant neoplasm of other sites of tongue
41571	B495.00	Malignant neoplasm of bladder neck
41691	B562000	Secondary and unspec malig neop coeliac lymph nodes
41931	B550100	Malignant neoplasm of cheek NOS
42012	B494.00	Malignant neoplasm of posterior wall of urinary bladder
42023	B497.00	Malignant neoplasm of urachus
42070	B345.00	Malignant neoplasm of lower-outer quadrant of female breast
42153	B32y.00	Malignant melanoma of other specified skin site
42193	B115.00	Malignant neoplasm of lesser curve of stomach unspecified
42218	B55y.00	Malignant neoplasm of other specified sites
42416	B105.00	Malignant neoplasm of lower third of oesophagus
42426	B511.00	Malignant neoplasm of frontal lobe
42460	B543.00	Malignant neoplasm of pineal gland
42461	B61zz00	Hodgkin's disease NOS

42539	B670.00	Acute erythraemia and erythroleukaemia
42566	B224z00	Malignant neoplasm of lower lobe, bronchus or lung NOS
42569	B2zz.00	Malignant neoplasm of respiratory tract NOS
42579	B62y300	Malignant lymphoma NOS of intra-abdominal lymph nodes
42714	B327500	Malignant melanoma of ankle
42856	B200z00	Malignant neoplasm of nasal cavities NOS
43111	B213.00	Malignant neoplasm of laryngeal cartilage
43151	Byu3300	[X]Malignant neoplasm/bone+articular cartilage, unspecified
43200	B06z.00	Malignant neoplasm of oropharynx NOS
43390	B12z.00	Malignant neoplasm of small intestine NOS
43392	B483.00	Malignant neoplasm of penis, part unspecified
43400	B03..00	Malignant neoplasm of gum
43415	ByuD000	[X]Other Hodgkin's disease
43431	B010.00	Malignant neoplasm of base of tongue
43435	B41yz00	Malignant neoplasm of other site of cervix NOS
43450	B63z.00	Immunoproliferative neoplasm or myeloma NOS
43463	B325700	Malignant melanoma of back
43475	B310.00	Malig neop of connective and soft tissue head, face and neck
43479	B121.00	Malignant neoplasm of jejunum
43490	Byu1100	[X]Other specified carcinomas of liver
43548	B080.00	Malignant neoplasm of postcricoid region
43552	B630.11	Kahler's disease
43572	B114.00	Malignant neoplasm of body of stomach
43614	B30X.00	Malignant neoplasm/bones+articular cartilage/limb,unspfd
43642	B011.00	Malignant neoplasm of dorsal surface of tongue
43715	B325600	Malignant melanoma of umbilicus
43761	B451.00	Malignant neoplasm of labia majora
43781	B011z00	Malignant neoplasm of dorsum of tongue NOS
43930	B582000	Secondary malignant neoplasm of skin of head

43940	B431.00	Malignant neoplasm of isthmus of uterine body
44089	B517.00	Malignant neoplasm of brain stem
44108	B18..00	Malignant neoplasm of retroperitoneum and peritoneum
44139	B073.00	Malignant neoplasm of anterior wall of nasopharynx
44169	B222z00	Malignant neoplasm of upper lobe, bronchus or lung NOS
44196	B611.00	Hodgkin's granuloma
44267	B623.00	Malignant histiocytosis
44318	B62xX00	Oth and unspecif peripheral & cutaneous T-cell lymphomas
44356	B2z..00	Malig neop other/ill-defined sites resp/intrathoracic organs
44399	B150z00	Primary malignant neoplasm of liver NOS
44452	B300C00	Malignant neoplasm of vomer
44529	B575.00	Secondary malignant neoplasm of large intestine and rectum
44609	B306000	Malignant neoplasm of ilium
44615	B586.00	Secondary malignant neoplasm of ovary
44627	B560800	Secondary and unspec malig neop anterior cervical LN
44805	B312100	Malig neop of connective and soft tissue thigh and upper leg
44884	B4Ay.00	Malignant neoplasm of other urinary organs
44931	B562z00	Secondary and unspec malig neop intra-abdominal LN NOS
44996	B491.00	Malignant neoplasm of dome of urinary bladder
45071	B314.00	Malignant neoplasm of connective and soft tissue of abdomen
45139	B323400	Malignant melanoma of external surface of nose
45154	B516.00	Malignant neoplasm of cerebellum
45222	B343.00	Malignant neoplasm of lower-inner quadrant of female breast
45260	Byu9000	[X]Malignant neoplasm of urinary organ, unspecified
45262	Byu8200	[X]Malignant neoplasm of male genital organ, unspecified
45264	B620100	Nodular lymphoma of lymph nodes of head, face and neck
45267	B55z.00	Malignant neoplasm of other and ill defined site NOS
45306	B324100	Malignant melanoma of neck
45307	B2...11	Carcinoma of respiratory tract and intrathoracic organs

45408	B040.00	Malignant neoplasm of anterior portion of floor of mouth
45490	B430z00	Malignant neoplasm of corpus uteri NOS
45667	B501.00	Malignant neoplasm of orbit
45700	By...00	Neoplasms otherwise specified
45755	B326200	Malignant melanoma of fore-arm
45760	B325z00	Malignant melanoma of trunk, excluding scrotum, NOS
45766	Byu1200	[X]Malignant neoplasm of intestinal tract, part unspecified
45793	B430300	Malignant neoplasm of myometrium of corpus uteri
45824	B58y900	Secondary malignant neoplasm of tongue
45922	B508.00	Malignant neoplasm, overlapping lesion of eye and adnexa
45986	B041.00	Malignant neoplasm of lateral portion of floor of mouth
46042	B630300	Lambda light chain myeloma
46114	B0z..00	Malig neop other/ill-defined sites lip, oral cavity, pharynx
46153	B443.00	Malignant neoplasm of parametrium
46159	B142000	Malignant neoplasm of cloacogenic zone
46255	B327.00	Malignant melanoma of lower limb and hip
46409	B563300	Secondary and unspec malig neop pectoral lymph nodes
46548	B071100	Malignant neoplasm of pharyngeal tonsil
46613	B18y.00	Malignant neoplasm of specified parts of peritoneum
46728	B064.00	Malignant neoplasm of anterior epiglottis
46789	B515000	Malignant neoplasm of choroid plexus
46792	B512.00	Malignant neoplasm of temporal lobe
46905	B545200	Malignant neoplasm of coccygeal body
46939	B302000	Malignant neoplasm of cervical vertebra
47094	B323200	Malignant melanoma of eyebrow
47204	B625z00	Letterer-Siwe disease NOS
47205	B017.00	Malignant overlapping lesion of tongue
47252	B323.00	Malignant melanoma of other and unspecified parts of face
47286	B551.00	Malignant neoplasm of thorax

47366	B565300	Secondary and unspec malig neop sacral lymph nodes
47556	B512z00	Malignant neoplasm of temporal lobe NOS
47633	ByuA300	[X]Malig neopl, overlap lesion brain & other part of CNS
47668	B48y100	Malignant neoplasm of tunica vaginalis
47767	B486.00	Malignant neoplasm of scrotum
47801	B49y000	Malignant neoplasm, overlapping lesion of bladder
47810	B59..00	Malignant neoplasm of unspecified site
47840	B545100	Malignant neoplasm of aortic body
47862	B213300	Malignant neoplasm of thyroid cartilage
47899	B451000	Malignant neoplasm of greater vestibular (Bartholin's) gland
48073	B510000	Malignant neoplasm of basal ganglia
48231	B13y.00	Malignant neoplasm of other specified sites of colon
48237	B111000	Malignant neoplasm of prepylorus of stomach
48517	B310200	Malignant neoplasm of soft tissue of neck
48519	B065.00	Malignant neoplasm of junctional region of epiglottis
48537	B17y.00	Malignant neoplasm of other specified sites of pancreas
48743	B482.00	Malignant neoplasm of body of penis
48809	B35zz00	Malignant neoplasm of male breast NOS
48820	B410.00	Malignant neoplasm of endocervix
48828	B582500	Secondary malignant neoplasm of skin of hip and leg
49054	B304000	Malignant neoplasm of scapula
49132	B517100	Malignant neoplasm of medulla oblongata
49145	B58y700	Secondary malignant neoplasm of penis
49148	B347.00	Malignant neoplasm, overlapping lesion of breast
49214	B560.00	Secondary and unspec malig neop lymph nodes head/face/neck
49262	B627200	Follicular non-Hodgkin's large cell lymphoma
49292	Byu1300	[X]Malignant neoplsm/ill-defin sites within digestive system
49301	B6z..00	Malignant neoplasm lymphatic or haematopoietic tissue NOS
49360	B031.00	Malignant neoplasm of lower gum

49400	B430211	Malignant neoplasm of endometrium
49463	B310400	Malignant neoplasm of tarsus of eyelid
49491	B303100	Malignant neoplasm of sternum
49525	B59zX00	Kaposi's sarcoma, unspecified
49605	B615.00	Hodgkin's disease, mixed cellularity
49701	B302z00	Malignant neoplasm of vertebral column NOS
49714	B523.00	Malignant neoplasm of spinal meninges
49725	B64y.00	Other lymphoid leukaemia
49758	B0zy.00	Malignant neoplasm of other sites lip, oral cavity, pharynx
49814	B325000	Malignant melanoma of axilla
49828	B441.00	Malignant neoplasm of fallopian tube
49875	B52X.00	Malignant neoplasm of meninges, unspecified
50035	B545.00	Malignant neoplasm of aortic body and other paraganglia
50152	B306500	Malignant sacral teratoma
50199	B563.00	Secondary and unspec malig neop axilla and upper limb LN
50222	B311000	Malignant neoplasm of connective and soft tissue of shoulder
50285	B410z00	Malignant neoplasm of endocervix NOS
50289	B241z00	Malignant neoplasm of heart NOS
50290	B6z0.00	Kaposi's sarcoma of lymph nodes
50292	Byu2500	[X]Malignant neoplasm of mediastinum, part unspecified
50296	B000100	Malignant neoplasm of upper lip, lipstick area
50297	B411.00	Malignant neoplasm of exocervix
50298	B300500	Malignant neoplasm of orbital bone
50299	B300900	Malignant neoplasm of zygomatic bone
50402	B307100	Malignant neoplasm of fibula
50475	B02z.00	Malignant neoplasm of major salivary gland NOS
50505	B326000	Malignant melanoma of shoulder
50579	B214.00	Malignant neoplasm, overlapping lesion of larynx
50668	B627300	Diffuse non-Hodgkin's small cell (diffuse) lymphoma

50681	B480.00	Malignant neoplasm of prepuce (foreskin)
50695	B627500	Diffuse non-Hodgkin mixed sml & lge cell (diffuse) lymphoma
50696	B62y100	Malignant lymphoma NOS of lymph nodes of head, face and neck
50777	B524600	Malignant neoplasm,overlap lesion periph nerve & auton ns
50789	B103.00	Malignant neoplasm of upper third of oesophagus
50858	B674.00	Acute panmyelosis
50898	B18y300	Malignant neoplasm of omentum
50904	B563200	Secondary and unspec malig neop infraclavicular lymph nodes
50974	B14z.00	Malignant neoplasm rectum,rectosigmoid junction and anus NOS
51115	B522.00	Malignant neoplasm of spinal cord
51209	B325800	Malignant melanoma of chest wall
51237	B303z00	Malignant neoplasm of rib, sternum and clavicle NOS
51255	B1zz.00	Malignant neoplasm of digestive tract and peritoneum NOS
51352	B592.00	Malignant neoplasms of independent (primary) multiple sites
51551	B571.00	Secondary malignant neoplasm of mediastinum
51690	B117.00	Malignant neoplasm, overlapping lesion of stomach
51786	B021.00	Malignant neoplasm of submandibular gland
51795	B545000	Malignant neoplasm of glomus jugulare
51818	B550300	Malignant neoplasm of jaw NOS
51873	B327100	Malignant melanoma of thigh
51921	B306200	Malignant neoplasm of pubis
51926	B062000	Malignant neoplasm of faucial pillar
51965	B315.00	Malignant neoplasm of connective and soft tissue of pelvis
52029	ByuC800	[X]Malignant neoplasm without specification of site
52190	B561900	Secondary and unspec malig neop pulmonary lymph nodes
52316	B553.00	Malignant neoplasm of pelvis
52327	B653000	Chloroma
52511	B515.00	Malignant neoplasm of cerebral ventricles
52537	B161100	Malignant neoplasm of hepatic duct

52570	B487.00	Malignant neoplasm, overlapping lesion of penis
52594	B4z..00	Malignant neoplasm of genitourinary organ NOS
52736	B562.00	Secondary and unspec malig neop intra-abdominal lymph nodes
53103	B410100	Malignant neoplasm of endocervical gland
53369	B327900	Malignant melanoma of great toe
53397	B61z.00	Hodgkin's disease NOS
53504	B52W.00	Malig neopl, overlap lesion brain & other part of CNS
53528	B581200	Secondary malignant neoplasm of urethra
53551	B627600	Diffuse non-Hodgkin's immunoblastic (diffuse) lymphoma
53591	B10y.00	Malignant neoplasm of other specified part of oesophagus
53594	B300000	Malignant neoplasm of ethmoid bone
53599	B300100	Malignant neoplasm of frontal bone
53629	B325200	Malignant melanoma of buttock
53884	B060z00	Malignant neoplasm tonsil NOS
53910	B453.00	Malignant neoplasm of clitoris
53989	B311.00	Malig neop connective and soft tissue upper limb/shoulder
54083	B625800	Letterer-Siwe disease of lymph nodes of multiple sites
54103	B16..00	Malignant neoplasm gallbladder and extrahepatic bile ducts
54120	B584.00	Secondary malignant neoplasm of other part of nervous system
54133	B510z00	Malignant neoplasm of cerebrum NOS
54134	B223z00	Malignant neoplasm of middle lobe, bronchus or lung NOS
54171	B104.00	Malignant neoplasm of middle third of oesophagus
54184	B4A1z00	Malignant neoplasm of renal pelvis NOS
54186	B313100	Malignant neoplasm of diaphragm
54202	B35z.00	Malignant neoplasm of other site of male breast
54222	B312400	Malignant neoplasm of connective and soft tissue of foot
54253	ByuC700	[X]Secondary malignant neoplasm of other specified sites
54267	B59z.00	Malignant neoplasm of unspecified site NOS
54278	B564000	Secondary and unspec malig neop superficial inguinal LN

54305	B327200	Malignant melanoma of knee
54493	B303500	Malignant neoplasm of xiphoid process
54494	B350.00	Malignant neoplasm of nipple and areola of male breast
54613	B201200	Malignant neoplasm of tympanic antrum
54631	B306.00	Malignant neoplasm of pelvic bones, sacrum and coccyx
54632	B321.00	Malignant melanoma of eyelid including canthus
54636	B203.00	Malignant neoplasm of ethmoid sinus
54679	B594.00	Secondary malignant neoplasm of unknown site
54685	B326100	Malignant melanoma of upper arm
54691	B302200	Malignant neoplasm of lumbar vertebra
54747	B300600	Malignant neoplasm of parietal bone
54793	B682.00	Subacute leukaemia NOS
54956	B50z.00	Malignant neoplasm of eye NOS
54965	B312200	Malig neop connective and soft tissue of popliteal space
55015	B05z.00	Malignant neoplasm of mouth NOS
55019	B11y.00	Malignant neoplasm of other specified site of stomach
55066	B062.00	Malignant neoplasm of tonsillar pillar
55090	B58y100	Secondary malignant neoplasm of uterus
55096	B582z00	Secondary malignant neoplasm of skin NOS
55098	B550000	Malignant neoplasm of head NOS
55101	B553z00	Malignant neoplasm of pelvis NOS
55246	B20z.00	Malignant neoplasm of accessory sinus NOS
55292	B326z00	Malignant melanoma of upper limb or shoulder NOS
55303	B614100	Hodgkin's nodular sclerosis of head, face and neck
55374	B215.00	Malignant neoplasm of epiglottis NOS
55434	B116.00	Malignant neoplasm of greater curve of stomach unspecified
55463	B561400	Secondary and unspec malig neop post mediastinal lymph nodes
55588	Byu7300	[X]Malignant neoplasm of female genital organ, unspecified
55595	B300700	Malignant neoplasm of sphenoid bone

55630	B07y.00	Malignant neoplasm of other specified site of nasopharynx
55659	B14y.00	Malig neop other site rectum, rectosigmoid junction and anus
55881	B324000	Malignant melanoma of scalp
55946	B574000	Secondary malignant neoplasm of duodenum
55953	B300400	Malignant neoplasm of occipital bone
56345	B57y.00	Secondary malignant neoplasm of other digestive organ
56355	B066.00	Malignant neoplasm of lateral wall of oropharynx
56490	B52z.00	Malignant neoplasm of nervous system NOS
56513	B307000	Malignant neoplasm of femur
56709	B04y.00	Malignant neoplasm of other sites of floor of mouth
56715	B34y.00	Malignant neoplasm of other site of female breast
56718	B500z00	Malignant neoplasm of eyeball NOS
56918	B1zy.00	Malignant neoplasm other spec digestive tract and peritoneum
56925	Byu4000	[X]Malignant melanoma of other+unspecified parts of face
57047	B544.00	Malignant neoplasm of carotid body
57191	Byu8000	[X]Malignant neoplasm/other specified male genital organs
57225	B614000	Hodgkin's disease, nodular sclerosis of unspecified site
57235	B410000	Malignant neoplasm of endocervical canal
57248	B082.00	Malignant neoplasm aryepiglottic fold, hypopharyngeal aspect
57260	B322.00	Malignant melanoma of ear and external auricular canal
57427	B62y000	Malignant lymphoma NOS of unspecified site
57471	B316.00	Malig neop of connective and soft tissue trunk unspecified
57481	ByuC300	[X]Secondary malignant neoplasm/oth+unspc respiratory organs
57482	B311200	Malignant neoplasm of connective and soft tissue of fore-arm
57671	B672.00	Megakaryocytic leukaemia
57719	B41y100	Malignant neoplasm of squamocolumnar junction of cervix
57737	B62x100	Lymphoepithelioid lymphoma
57756	Byu7100	[X]Malignant neoplasm/other specified female genital organs
57854	B553000	Malignant neoplasm of inguinal region NOS

57988	B305000	Malignant neoplasm of carpal bone - scaphoid
58061	B452.00	Malignant neoplasm of labia minora
58082	B620800	Nodular lymphoma of lymph nodes of multiple sites
58088	B151400	Malignant neoplasm of intrahepatic gall duct
58094	B412.00	Malignant neoplasm, overlapping lesion of cervix uteri
58121	B014.00	Malignant neoplasm of anterior 2/3 of tongue unspecified
58684	B615200	Hodgkin's mixed cellularity of intrathoracic lymph nodes
58692	B561500	Secondary and unspec malig neop paratracheal lymph nodes
58836	B315z00	Malig neop of connective and soft tissue of pelvis NOS
58871	B623z00	Malignant histiocytosis NOS
58903	B550z00	Malignant neoplasm of head, neck and face NOS
58949	B308D00	Malignant neoplasm of phalanges of foot
58958	B323500	Malignant melanoma of temple
58962	B62x500	Malignant immunoproliferative small intestinal disease
58973	Byu0.00	[X]Malignant neoplasm of lip, oral cavity and pharynx
59004	B072.00	Malignant neoplasm of lateral wall of nasopharynx
59036	B300.00	Malignant neoplasm of bones of skull and face
59041	B500000	Malignant neoplasm of ciliary body
59061	B322000	Malignant melanoma of auricle (ear)
59092	B111z00	Malignant neoplasm of pylorus of stomach NOS
59097	B431000	Malignant neoplasm of lower uterine segment
59115	B602100	Burkitt's lymphoma of lymph nodes of head, face and neck
59152	B315200	Malignant neoplasm of connective and soft tissue of perineum
59170	B51y000	Malignant neoplasm of corpus callosum
59223	B306100	Malignant neoplasm of ischium
59286	B4Ay000	Malignant neoplasm of overlapping lesion of urinary organs
59362	B451z00	Malignant neoplasm of labia majora NOS
59375	B583z00	Secondary malignant neoplasm of brain or spinal cord NOS
59381	B500100	Malignant neoplasm of iris

59382	B310000	Malignant neoplasm of soft tissue of head
59388	B18y100	Malignant neoplasm of mesocaecum
59520	B300200	Malignant neoplasm of malar bone
59718	B542z00	Malig neop pituitary gland or craniopharyngeal duct NOS
59755	B61z200	Hodgkin's disease NOS of intrathoracic lymph nodes
59778	B61z100	Hodgkin's disease NOS of lymph nodes of head, face and neck
59823	B542.00	Malignant neoplasm pituitary gland and craniopharyngeal duct
59831	B340z00	Malignant neoplasm of nipple or areola of female breast NOS
60035	B310300	Malignant neoplasm of cartilage of ear
60052	B55yz00	Malignant neoplasm of specified site NOS
60053	Byu..00	[X]Additional neoplasm classification terms
60092	B62y700	Malignant lymphoma NOS of spleen
60134	B581000	Secondary malignant neoplasm of ureter
60162	Byu5A00	[X]Malignant neoplasm overlapping lesion of skin
60242	B600000	Reticulosarcoma of unspecified site
60247	B314z00	Malig neop of connective and soft tissue of abdomen NOS
60312	B16y.00	Malignant neoplasm other gallbladder/extrahepatic bile duct
60335	B58y400	Secondary malignant neoplasm of vulva
60403	B303300	Malignant neoplasm of costal cartilage
60772	B450z00	Malignant neoplasm of vagina NOS
61064	B24X.00	Malignant neoplasm of mediastinum, part unspecified
61149	B614300	Hodgkin's nodular sclerosis of intra-abdominal lymph nodes
61246	B327600	Malignant melanoma of heel
61289	B564100	Secondary and unspec malig neop deep inguinal lymph nodes
61390	B540000	Malignant neoplasm of adrenal cortex
61399	B510100	Malignant neoplasm of cerebral cortex
61500	B690.00	Acute myelomonocytic leukaemia
61510	B062200	Malignant neoplasm of palatoglossal arch
61555	B180z00	Malignant neoplasm of retroperitoneum NOS

61643	B151z00	Malignant neoplasm of intrahepatic bile ducts NOS
61662	B61z000	Hodgkin's disease NOS, unspecified site
61677	B562200	Secondary and unspec malig neop inferior mesenteric LN
61692	B004.00	Malignant neoplasm of lip unspecified, inner aspect
61693	ByuD600	[X]Other myeloid leukaemia
61695	B100.00	Malignant neoplasm of cervical oesophagus
61716	B524100	Malignant neoplasm of peripheral nerve,upp limb,incl should
61741	B304200	Malignant neoplasm of humerus
62104	B300800	Malignant neoplasm of temporal bone
62124	B561800	Secondary and unspec malig neop bronchopulmonary lymph nodes
62126	B510500	Malignant neoplasm of thalamus
62182	B200300	Malignant neoplasm of vestibule of nose
62380	B601200	Lymphosarcoma of intrathoracic lymph nodes
62437	B62x400	Malignant reticulosis
62475	B326300	Malignant melanoma of hand
62556	B24..00	Malignant neoplasm of thymus, heart and mediastinum
62584	B573.00	Secondary malignant neoplasm of other respiratory organs
62630	B307z00	Malignant neoplasm of long bones of leg NOS
62761	B200200	Malignant neoplasm of septum of nose
62828	B581z00	Secondary malignant neoplasm of other urinary organ NOS
62840	B013.00	Malignant neoplasm of ventral surface of tongue
62909	B575100	Secondary malignant neoplasm of rectum
63054	B614z00	Hodgkin's disease, nodular sclerosis NOS
63104	B501z00	Malignant neoplasm of orbit NOS
63105	B62y500	Malignant lymphoma NOS of lymph node inguinal region and leg
63224	B48z.00	Malignant neoplasm of penis and other male genital organ NOS
63300	Byu3200	[X]Malignant neoplasm/overlap lesion/bone+articulr cartilage
63331	B485.00	Malignant neoplasm of spermatic cord
63375	ByuDE00	[X]Unspecified B-cell non-Hodgkin's lymphoma

63430	B241000	Malignant neoplasm of endocardium
63460	B213000	Malignant neoplasm of arytenoid cartilage
63470	B102.00	Malignant neoplasm of abdominal oesophagus
63475	B652.00	Subacute myeloid leukaemia
63568	B524000	Malignant neoplasm of peripheral nerves of head, face & neck
63598	ByuE.00	[X]Malignant neoplasms/independent (primary) multiple sites
63625	B616400	Hodgkin's lymphocytic depletion lymph nodes axilla and arm
63653	B671.11	Heilmeyer - Schoner disease
63657	B503.00	Malignant neoplasm of conjunctiva
63695	B524300	Malignant neoplasm of peripheral nerve of thorax
63723	B601z00	Lymphosarcoma NOS
63896	B582400	Secondary malignant neoplasm of skin of shoulder and arm
63915	B564.00	Secondary and unspec malig neop inguinal and lower limb LN
63925	ByuA200	[X]Malignant neoplasm of meninges, unspecified
63979	B013100	Malignant neoplasm of frenulum linguae
63988	B311500	Malignant neoplasm of connective and soft tissue of thumb
63995	B123.00	Malignant neoplasm of Meckel's diverticulum
63997	B326500	Malignant melanoma of thumb
64036	B612.00	Hodgkin's sarcoma
64106	B18yz00	Malignant neoplasm of specified parts of peritoneum NOS
64116	B561.00	Secondary and unspec malig neop intrathoracic lymph nodes
64195	B54z.00	Malig neop of endocrine gland or related structure NOS
64309	ByuB100	[X]Malignant neoplasm of endocrine gland, unspecified
64327	B327z00	Malignant melanoma of lower limb or hip NOS
64336	ByuD300	[X]Other specified types of non-Hodgkin's lymphoma
64345	B311100	Malignant neoplasm of connective and soft tissue, upper arm
64427	B62z100	Unspec malig neop lymphoid/histiocytic lymph node head/neck
64462	B083.00	Malignant neoplasm of posterior pharynx
64497	Byu7000	[X]Malignant neoplasm of uterine adnexa, unspecified

64515	ByuDC00	[X]Diffuse non-Hodgkin's lymphoma, unspecified
64516	B18y400	Malignant neoplasm of parietal peritoneum
64557	B517000	Malignant neoplasm of cerebral peduncle
64567	B63y.00	Other immunoproliferative neoplasms
64602	B470.00	Malignant neoplasm of undescended testis
64670	B601300	Lymphosarcoma of intra-abdominal lymph nodes
64680	B574.00	Secondary malignant neoplasm of small intestine and duodenum
64686	B340100	Malignant neoplasm of areola of female breast
64810	B551z00	Malignant neoplasm of thorax NOS
64817	B502.00	Malignant neoplasm of lacrimal gland
64848	B304400	Malignant neoplasm of ulna
64897	ByuE000	[X]Malignant neoplasms/independent (primary) multiple sites
64918	B560000	Secondary and unspec malig neop of superficial parotid LN
64971	B520000	Malignant neoplasm of olfactory bulb
65106	B44z.00	Malignant neoplasm of uterine adnexa NOS
65122	B624000	Leukaemic reticuloendotheliosis of unspecified sites
65123	B624300	Leukaemic reticuloend of intra-abdominal lymph nodes
65124	B151000	Malignant neoplasm of interlobular bile ducts
65159	B180100	Malignant neoplasm of perinephric tissue
65164	B326.00	Malignant melanoma of upper limb and shoulder
65165	ByuD900	[X]Other leukaemia of unspecified cell type
65180	B627800	Diffuse non-Hodgkin's lymphoma undifferentiated (diffuse)
65215	B205.00	Malignant neoplasm of sphenoidal sinus
65233	B31y.00	Malig neop connective and soft tissue other specified site
65241	B51y200	Malignant neoplasm, overlapping lesion of brain
65253	B560300	Secondary and unspec malignant neoplasm occipital lymph node
65312	B11y000	Malignant neoplasm of anterior wall of stomach NEC
65357	B507100	Malignant neoplasm of nasolacrimal duct
65372	B11yz00	Malignant neoplasm of other specified site of stomach NOS

65434	B62z.00	Malignant neoplasms of lymphoid and histiocytic tissue NOS
65458	B52..00	Malig neop of other and unspecified parts of nervous system
65460	B1z1.00	Malignant neoplasm of spleen NEC
65466	B592X00	Kaposi's sarcoma of multiple organs
65483	B614400	Hodgkin's nodular sclerosis of lymph nodes of axilla and arm
65489	B610.00	Hodgkin's paragranuloma
65490	B58y411	Secondary cancer of the vulva
65599	B520200	Malignant neoplasm of acoustic nerve
65605	B241200	Malignant neoplasm of myocardium
65625	B324.00	Malignant melanoma of scalp and neck
65642	B623300	Malignant histiocytosis of intra-abdominal lymph nodes
65701	B620z00	Nodular lymphoma NOS
65721	B673.00	Mast cell leukaemia
65777	B672.11	Thrombocytic leukaemia
65793	B2z0.00	Malig neop of upper respiratory tract, part unspecified
65880	B304z00	Malig neop of scapula and long bones of upper arm NOS
66083	B57z.00	Secondary malig neop of respiratory or digestive system NOS
66088	B312.00	Malig neop of connective and soft tissue of hip and leg
66089	B65yz00	Other myeloid leukaemia NOS
66163	ByuC200	[X]2ndry+unspcf malignant neoplasm lymph nodes/multi regions
66166	B124.00	Malignant neoplasm, overlapping lesion of small intestine
66270	B000000	Malignant neoplasm of upper lip, external
66327	B620000	Nodular lymphoma of unspecified site
66384	B001000	Malignant neoplasm of lower lip, external
66422	B074.00	Malignant neoplasm, overlapping lesion of nasopharynx
66444	Byu2100	[X]Malignant neoplasm/overlap lesion/heart,mediastinm+pleura
66488	B314000	Malig neop of connective and soft tissue of abdominal wall
66639	B303200	Malignant neoplasm of clavicle
66646	B26..00	Malignant neoplasm, overlap lesion of resp & intrathor orgs

66750	B24z.00	Malignant neoplasm of heart, thymus and mediastinum NOS
66775	B560100	Secondary and unspec malignant neoplasm mastoid lymph nodes
66908	B306400	Malignant neoplasm of coccygeal vertebra
67029	ByuD500	[X]Other lymphoid leukaemia
67034	Byu5000	[X]Mesothelioma of other sites
67107	B230.00	Malignant neoplasm of parietal pleura
67129	B560z00	Secondary unspec malig neop lymph nodes head/face/neck NOS
67211	B523z00	Malignant neoplasm of spinal meninges NOS
67217	B55y100	Malignant neoplasm of trunk NOS
67236	B512000	Malignant neoplasm of hippocampus
67323	B06y.00	Malignant neoplasm of oropharynx, other specified sites
67324	B315100	Malig neop of connective and soft tissue of inguinal region
67396	B576.00	Secondary malig neop of retroperitoneum and peritoneum
67446	B001.00	Malignant neoplasm of lower lip, vermilion border
67451	B30W.00	Malignant neoplasm/overlap lesion/bone+articulr cartilage
67497	B106.00	Malignant neoplasm, overlapping lesion of oesophagus
67504	B003000	Malignant neoplasm of lower lip, buccal aspect
67506	B614200	Hodgkin's nodular sclerosis of intrathoracic lymph nodes
67518	ByuD100	[X]Other types of follicular non-Hodgkin's lymphoma
67700	B66..12	Monoblastic leukaemia
67703	B616.00	Hodgkin's disease, lymphocytic depletion
67763	B303400	Malignant neoplasm of costo-vertebral joint
67797	B561600	Secondary and unspec malig neop superfic tracheobronchial LN
67806	B323z00	Malignant melanoma of face NOS
67884	B350100	Malignant neoplasm of areola of male breast
67949	B48y.00	Malignant neoplasm of other male genital organ
68027	ByuA000	[X]Malignant neoplasm/other and unspecified cranial nerves
68039	B612400	Hodgkin's sarcoma of lymph nodes of axilla and upper limb
68055	B307.00	Malignant neoplasm of long bones of leg

68133	B323300	Malignant melanoma of forehead
68155	B430100	Malignant neoplasm of fundus of corpus uteri
68161	B48y000	Malignant neoplasm of seminal vesicle
68236	B550.00	Malignant neoplasm of head, neck and face
68330	B613100	Hodgkin's, lymphocytic-histiocytic pred of head, face, neck
68332	ByuC600	[X]2ndry malignant neoplasm/oth+unspec parts/nervous system
68399	B004200	Malignant neoplasm of lip unspecified, mucosa
68410	B150200	Primary angiosarcoma of liver
68480	B350000	Malignant neoplasm of nipple of male breast
68611	B560900	Secondary and unspec malig neop deep cervical LN
68641	B517z00	Malignant neoplasm of brain stem NOS
68787	B55y000	Malignant neoplasm of back NOS
68824	B48y200	Malignant neoplasm, overlapping lesion male genital orgs
69104	B305100	Malignant neoplasm of carpal bone - lunate
69132	B562400	Secondary and unspec malig neop external iliac lymph nodes
69146	B300z00	Malignant neoplasm of bones of skull and face NOS
69392	B561700	Secondary and unspec malig neop inferior tracheobronchial LN
69497	B623000	Malignant histiocytosis of unspecified site
69671	B010.11	Malignant neoplasm of posterior third of tongue
69761	B00zz00	Malignant neoplasm of lip, vermilion border NOS
69821	B18y600	Malignant neoplasm of the pouch of Douglas
69927	B308800	Malignant neoplasm of first metatarsal bone
69951	B055100	Malignant neoplasm of roof of mouth
70026	B574z00	Secondary malig neop of small intestine or duodenum NOS
70104	B521z00	Malignant neoplasm of cerebral meninges NOS
70126	B520100	Malignant neoplasm of optic nerve
70374	B600300	Reticulosarcoma of intra-abdominal lymph nodes
70463	B315000	Malignant neoplasm of connective and soft tissue of buttock
70509	B627D00	Diffuse non-Hodgkin's centroblastic lymphoma

70637	B320.00	Malignant melanoma of lip
70696	B02y.00	Malignant neoplasm of other major salivary glands
70716	B62zz11	Immunoproliferative neoplasm
70724	B653.00	Myeloid sarcoma
70729	B431z00	Malignant neoplasm of isthmus of uterine body NOS
70736	B58y300	Secondary malignant neoplasm of vagina
70747	B564z00	Secondary and unspec malig neop of inguinal and leg LN NOS
70819	B055.00	Malignant neoplasm of palate unspecified
70824	B540z00	Malignant neoplasm of adrenal gland NOS
70842	B627100	Follicular non-Hodg mixed sml cleavd & lge cell lymphoma
70928	B022.00	Malignant neoplasm of sublingual gland
70942	B510400	Malignant neoplasm of hypothalamus
71031	B600100	Reticulosarcoma of lymph nodes of head, face and neck
71136	B323100	Malignant melanoma of chin
71139	B51y.00	Malignant neoplasm of other parts of brain
71142	B613000	Hodgkin's, lymphocytic-histiocytic predominance unspec site
71147	B003.00	Malignant neoplasm of lower lip, inner aspect
71204	B200000	Malignant neoplasm of cartilage of nose
71238	B601100	Lymphosarcoma of lymph nodes of head, face and neck
71262	B62y600	Malignant lymphoma NOS of intrapelvic lymph nodes
71304	B602z00	Burkitt's lymphoma NOS
71584	B507.00	Malignant neoplasm of lacrimal duct
71609	B62z500	Unspec malig neop lymphoid/histiocytic nodes inguinal/leg
71625	B601000	Lymphosarcoma of unspecified site
71810	B304.00	Malignant neoplasm of scapula and long bones of upper arm
71946	B201300	Malignant neoplasm of mastoid air cells
72127	B484.00	Malignant neoplasm of epididymis
72174	B4A4.00	Malignant neoplasm of paraurethral glands
72197	B67y000	Lymphosarcoma cell leukaemia

72212	B308200	Malignant neoplasm of calcaneum
72224	B1z1100	Fibrosarcoma of spleen
72445	B161000	Malignant neoplasm of cystic duct
72464	B305.12	Malignant neoplasm of metacarpal bones
72500	ByuDB00	[X]Mal neoplasm/lymphoid,haematopoietic+related tissu,unspcf
72522	B313200	Malignant neoplasm of great vessels
72713	B562100	Secondary and unspec malig neop superficial mesenteric LN
72714	B621500	Mycosis fungoides of lymph nodes of inguinal region and leg
72723	B430000	Malignant neoplasm of cornu of corpus uteri
72725	B62y200	Malignant lymphoma NOS of intrathoracic lymph nodes
72774	B642.00	Subacute lymphoid leukaemia
72803	B565z00	Secondary and unspec malig neop intrapelvic LN NOS
73213	B581.00	Secondary malignant neoplasm of other urinary organs
73296	Byu3100	[X]Malignant neoplasm/bones+articular cartilage/limb,unspfd
73439	B064z00	Malignant neoplasm of anterior epiglottis NOS
73510	B550500	Malignant neoplasm of supraclavicular fossa NOS
73530	B305.00	Malignant neoplasm of hand bones
73532	B613300	Hodgkin's, lymphocytic-histiocytic pred intra-abdominal node
73536	B327000	Malignant melanoma of hip
73537	B201z00	Malig neop auditory tube, middle ear, mastoid air cells NOS
73538	B563z00	Secondary and unspec malig neop axilla and upper limb LN NOS
73556	B305z00	Malignant neoplasm of hand bones NOS
73614	B004000	Malignant neoplasm of lip unspecified, buccal aspect
73616	B58y200	Secondary malignant neoplasm of cervix uteri
73718	B310z00	Malig neop connective and soft tissue head, face, neck NOS
73744	B322z00	Malignant melanoma of ear and external auricular canal NOS
73777	B624z00	Leukaemic reticuloendotheliosis NOS
73962	B000.00	Malignant neoplasm of upper lip, vermilion border
73988	B524500	Malignant neoplasm of peripheral nerve of pelvis

73992	B504.00	Malignant neoplasm of cornea
74896	B161z00	Malignant neoplasm of extrahepatic bile ducts NOS
84368	B565000	Secondary and unspec malig neop internal iliac lymph nodes
86046	B524400	Malignant neoplasm of peripheral nerve of abdomen
86812	B305D00	Malignant neoplasm of phalanges of hand
86996	B501000	Malignant neoplasm of connective tissue of orbit
86997	Byu2400	[X]Malignant neoplasm/ill-defined sites within resp system
87113	B54X.00	Malignant neoplasm-pluriglandular involvement,unspecified
87335	B624.12	Hairy cell leukaemia
88022	ByuC400	[X]Secondary malignant neoplasm/oth+unspcfd digestive organs
88144	B52y.00	Malignant neoplasm of other specified part of nervous system
88362	B08y.00	Malignant neoplasm of other specified hypopharyngeal site
89258	B524200	Malignant neoplasm of peripheral nerve of low limb, incl hip
89329	ByuD800	[X]Other specified leukaemias
89593	B151200	Malignant neoplasm of intrahepatic biliary passages
89657	B626z00	Malignant mast cell tumour NOS
89762	ByuD700	[X]Other monocytic leukaemia
89909	B003200	Malignant neoplasm of lower lip, mucosa
89916	B553100	Malignant neoplasm of presacral region
90124	B067.00	Malignant neoplasm of posterior wall of oropharynx
90201	B62x000	T-zone lymphoma
90290	B18y700	Malignant neoplasm of mesentery
90546	B312z00	Malig neop connective and soft tissue hip and leg NOS
90610	B002300	Malignant neoplasm of upper lip, oral aspect
90659	B54y.00	Malignant neoplasm of other specified endocrine gland
91035	B010z00	Malignant neoplasm of fixed part of tongue NOS
91037	B06yz00	Malignant neoplasm of other specified site of oropharynx NOS
91240	B517300	Malignant neoplasm of pons
91457	Byu5900	[X]Malignant neoplasm/connective + soft tissue,unspecified

91509	B471z00	Malignant neoplasm of descended testis NOS
91586	B311400	Malignant neoplasm of connective and soft tissue of finger
91674	B621300	Mycosis fungoides of intra-abdominal lymph nodes
91843	B003100	Malignant neoplasm of lower lip, frenulum
91895	B064100	Malignant neoplasm of glossoepiglottic fold
91896	Byu5800	[X]Mal neoplasm/connective+soft tissue of trunk,unspecified
91900	B61z400	Hodgkin's disease NOS of lymph nodes of axilla and arm
92068	B620300	Nodular lymphoma of intra-abdominal lymph nodes
92245	B613200	Hodgkin's, lymphocytic-histiocytic pred intrathoracic nodes
92329	B48yz00	Malignant neoplasm of other male genital organ NOS
92371	B304300	Malignant neoplasm of radius
92380	B602500	Burkitt's lymphoma of lymph nodes of inguinal region and leg
92382	B308B00	Malignant neoplasm of fourth metatarsal bone
92703	B560400	Secondary and unspec malig neop deep parotid lymph nodes
92720	B243.00	Malignant neoplasm of posterior mediastinum
93218	B03z.00	Malignant neoplasm of gum NOS
93342	B66z.00	Monocytic leukaemia NOS
93384	B62z200	Unspec malig neop lymphoid/histiocytic of intrathoracic node
93478	B138.00	Malignant neoplasm, overlapping lesion of colon
93537	B517200	Malignant neoplasm of midbrain
93665	Byu5300	[X]Kaposi's sarcoma, unspecified
93716	B561z00	Secondary and unspec malig neop intrathoracic LN NOS
93762	B42..00	Malignant neoplasm of placenta
93778	B1z1z00	Malignant neoplasm of spleen NOS
93842	B062300	Malignant neoplasm of palatopharyngeal arch
93951	B613500	Hodgkin's, lymphocytic-histiocytic pred inguinal and leg
94005	B615z00	Hodgkin's disease, mixed cellularity NOS
94174	B67y.00	Other and unspecified leukaemia
94220	B540100	Malignant neoplasm of adrenal medulla

94251	B00z100	Malignant neoplasm of lip, unspecified, lipstick area
94272	B314100	Malig neoplasm of connective and soft tissues of lumb spine
94278	B110111	Malignant neoplasm of gastro-oesophageal junction
94279	B61z700	Hodgkin's disease NOS of spleen
94355	B55y200	Malignant neoplasm of flank NOS
94390	B070.00	Malignant neoplasm of roof of nasopharynx
94407	B615100	Hodgkin's mixed cellularity of lymph nodes head, face, neck
94415	B623100	Malignant histiocytosis of lymph nodes head, face and neck
94427	B305C00	Malignant neoplasm of fifth metacarpal bone
94441	B003300	Malignant neoplasm of lower lip, oral aspect
94776	B1z2.00	Malignant neoplasm, overlapping lesion of digestive system
94975	B241300	Malignant neoplasm of pericardium
94995	B620500	Nodular lymphoma of lymph nodes of inguinal region and leg
95012	B621800	Mycosis fungoides of lymph nodes of multiple sites
95016	B0z1.00	Malignant neoplasm of Waldeyer's ring
95049	B616000	Hodgkin's lymphocytic depletion of unspecified site
95057	B34y000	Malignant neoplasm of ectopic site of female breast
95058	B600700	Reticulosarcoma of spleen
95182	B308100	Malignant neoplasm of talus
95323	B35z000	Malignant neoplasm of ectopic site of male breast
95338	B613600	Hodgkin's, lymphocytic-histiocytic pred intrapelvic nodes
95378	B561200	Secondary and unspec malig neop diaphragmatic lymph nodes
95421	B45y.00	Malignant neoplasm of other specified female genital organ
95429	B071.00	Malignant neoplasm of posterior wall of nasopharynx
95458	B300300	Malignant neoplasm of nasal bone
95480	B001100	Malignant neoplasm of lower lip, lipstick area
95505	B41y000	Malignant neoplasm of cervical stump
95545	B627911	Maltoma
95629	B325500	Malignant melanoma of perineum

95630	B62x600	True histiocytic lymphoma
95644	B241.00	Malignant neoplasm of heart
95671	Byu5700	[X]Malignant neoplasm of peritoneum, unspecified
95715	B627900	Mucosa-associated lymphoma
95772	B051000	Malignant neoplasm of upper buccal sulcus
95783	B17yz00	Malignant neoplasm of specified site of pancreas NOS
95792	B62zz00	Lymphoid and histiocytic malignancy NOS
95949	B621000	Mycosis fungoides of unspecified site
96003	B055000	Malignant neoplasm of junction of hard and soft palate
96094	B119.00	Siewert type III adenocarcinoma
96226	ByuC100	[X]Malignant neoplasm/overlap lesion/other+ill-defined sites
96379	B621400	Mycosis fungoides of lymph nodes of axilla and upper limb
96429	B470z00	Malignant neoplasm of undescended testis NOS
96445	B300B00	Malignant neoplasm of turbinate
96585	B32y000	Overlapping malignant melanoma of skin
96635	B17y000	Malignant neoplasm of ectopic pancreatic tissue
96782	B003z00	Malignant neoplasm of lower lip, inner aspect NOS
96783	B005.00	Malignant neoplasm of commissure of lip
96802	B11y100	Malignant neoplasm of posterior wall of stomach NEC
96869	B071z00	Malignant neoplasm of posterior wall of nasopharynx NOS
96971	B20y.00	Malig neop other site nasal cavity, middle ear and sinuses
97091	ByuC500	[X]2ndry malignant neoplasm/bladder+oth+unsp urinary organs
97332	B213z00	Malignant neoplasm of laryngeal cartilage NOS
97499	B118.00	Siewert type II adenocarcinoma
97530	B051100	Malignant neoplasm of lower buccal sulcus
97547	B551200	Malignant neoplasm of intrathoracic site NOS
97577	B602300	Burkitt's lymphoma of intra-abdominal lymph nodes
97672	B576z00	Secondary malig neop of retroperitoneum or peritoneum NOS
97746	B61z800	Hodgkin's disease NOS of lymph nodes of multiple sites

97832	B58y211	Secondary cancer of the cervix
97863	B615000	Hodgkin's disease, mixed cellularity of unspecified site
97875	B175.00	Malignant neoplasm, overlapping lesion of pancreas
97996	B44y.00	Malignant neoplasm of other site of uterine adnexa
98104	B23y.00	Malignant neoplasm of other specified pleura
98142	B107.00	Siewert type I adenocarcinoma
98361	Byu5B00	[X]Kaposi's sarcoma of other sites
98408	B313z00	Malig neop of connective and soft tissue of thorax NOS
98500	B002200	Malignant neoplasm of upper lip, mucosa
98537	B201100	Malignant neoplasm of tympanic cavity
98596	ByuD200	[X]Other types of diffuse non-Hodgkin's lymphoma
98626	B563100	Secondary and unspec malig neop supratrochlear lymph nodes
98740	B000z00	Malignant neoplasm of upper lip, vermilion border NOS
98813	B500.00	Malig neop eyeball excl conjunctiva, cornea, retina, choroid
98840	B610300	Hodgkin's paragranuloma of intra-abdominal lymph nodes
98909	B611100	Hodgkin's granuloma of lymph nodes of head, face and neck
98911	B200100	Malignant neoplasm of nasal conchae
99001	B002100	Malignant neoplasm of upper lip, frenulum
99012	B61z500	Hodgkin's disease NOS of lymph nodes inguinal region and leg
99015	B66y.00	Other monocytic leukaemia
99096	Byu2300	[X]Malignant neopl/overlapping les/resp+intrathoracic organs
99185	B062100	Malignant neoplasm of glossopalatine fold
99240	B600z00	Reticulosarcoma NOS
99257	B324z00	Malignant melanoma of scalp and neck NOS
99386	B073200	Malignant neoplasm posterior margin nasal septum and choanae
99413	B67yz00	Other and unspecified leukaemia NOS
99493	B002.00	Malignant neoplasm of upper lip, inner aspect
99511	B574200	Secondary malignant neoplasm of ileum
99572	B312500	Malignant neoplasm of connective and soft tissue of toe

99621	B520.00	Malignant neoplasm of cranial nerves
99887	B60y.00	Other specified reticulosarcoma or lymphosarcoma
99896	B12y.00	Malignant neoplasm of other specified site small intestine
99913	B510300	Malignant neoplasm of globus pallidus
99951	B60z.00	Reticulosarcoma or lymphosarcoma NOS
100002	B062z00	Malignant neoplasm of tonsillar fossa NOS
100006	B602200	Burkitt's lymphoma of intrathoracic lymph nodes
100083	B546.00	Neuroblastoma
100144	B004300	Malignant neoplasm of lip, oral aspect
100232	B24y.00	Malig neop of other site of heart, thymus and mediastinum
100296	B582100	Secondary malignant neoplasm of skin of face
100352	B601500	Lymphosarcoma of lymph nodes of inguinal region and leg
100423	B610100	Hodgkin's paragranuloma of lymph nodes of head, face, neck
100532	B622z00	Sezary's disease NOS
100584	B110000	Malignant neoplasm of cardiac orifice of stomach
100615	B626500	Mast cell malignancy of lymph nodes inguinal region and leg
100721	B002z00	Malignant neoplasm of upper lip, inner aspect NOS
100733	B51yz00	Malignant neoplasm of other part of brain NOS
100786	B651000	Chronic eosinophilic leukaemia
100906	B00z000	Malignant neoplasm of lip, unspecified, external
100918	B073z00	Malignant neoplasm of anterior wall of nasopharynx NOS
101086	B520z00	Malignant neoplasm of cranial nerves NOS
101114	B627A00	Diffuse non-Hodgkin's large cell lymphoma
101465	B62z800	Unspec malig neop lymphoid/histiocytic of multiple sites
101530	B616z00	Hodgkin's disease, lymphocytic depletion NOS
101606	B662.00	Subacute monocytic leukaemia
101608	B4A1100	Malignant neoplasm of ureteropelvic junction
101662	B565200	Secondary and unspec malig neop circumflex iliac LN
101668	Byu5400	[X]Malignant neoplasm/peripheral nerves of trunk,unspecified

101700	B139.00	Hereditary nonpolyposis colon cancer
101707	B001z00	Malignant neoplasm of lower lip, vermilion border NOS
101715	B616700	Hodgkin's disease, lymphocytic depletion of spleen
101753	B03y.00	Malignant neoplasm of other sites of gum
101778	B442.00	Malignant neoplasm of broad ligament
101805	B507000	Malignant neoplasm of lacrimal sac
101885	B241400	Mesothelioma of pericardium
101907	B182.00	Overlapping malign lesion of retroperitoneum and peritoneum
101988	B060100	Malignant neoplasm of palatine tonsil
102142	B013000	Malignant neoplasm of anterior 2/3 of tongue ventral surface
102145	B322100	Malignant melanoma of external auditory meatus
102151	B060200	Malignant neoplasm of overlapping lesion of tonsil
102158	B625200	Letterer-Siwe disease of intrathoracic lymph nodes
102205	B072z00	Malignant neoplasm of lateral wall of nasopharynx NOS
102594	B627E00	Diffuse large B-cell lymphoma
102688	ByuD400	[X]Other malignant immunoproliferative diseases
102715	B625000	Letterer-Siwe disease of unspecified sites
102783	B651200	Chronic neutrophilic leukaemia
102949	B312000	Malignant neoplasm of connective and soft tissue of hip
103245	B601700	Lymphosarcoma of spleen

Appendix 8 Ethics approval letter

NHS

National Research Ethics Service

NRES Committee Yorkshire & The Humber - Leeds East

Yorkshire and Humber REC Office
First Floor, Millside
Mill Pond Lane
Meanwood
Leeds
LS6 4RA

Telephone: 0113 3050106
Facsimile

22 November 2011

Dr A C Gadoud
Hull York Medical School
Hertford Building University of Hull
Hull
HU6 7RX

Dear Dr Gadoud

Study title:	**Perceptions of patients, carers and health care professionals regarding the transition to a palliative care approach in advanced heart failure**
REC reference:	**11/YH/0344**
Protocol number:	**N/A**

Thank you for your letter of 14 November 2011, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Ethical review of research sites

NHS sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Non-NHS sites

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned

Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of approvals from host organisations

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	Version	Date
GP/Consultant Information Sheets	6	12 August 2011
Investigator CV		12 August 2011
Letter from Sponsor		19 August 2011
Letter of invitation to Health Care Professionals	2.0	14 November 2011
Other: Supervisor CV (Johnson)		02 August 2011
Other: Supervisor CV (Macleod)		05 August 2011
Other: Indemnity arrangements Mr Jonathan Cant		07 July 2011
Other: Indemnity arrangements - Saint Catherine's Hospice		29 July 2011
Other: Indemnity arrangements - Dove House Hospice		18 July 2011
Other: Referees' or other scientific critique - Letter from consumer research panel		04 August 2011
Other: Referees' or other scientific critique - letter from Professor Karl Atkin		10 May 2011
Other: Topic guide: patient interview	6	12 August 2011
Other: Topic guide: carers interview	6	12 August 2011
Other: Topic guide: health care professionals interview	6	12 August 2011
Other: Topic guide: Health care professionals focus group	6	12 August 2011
Other: Proforma for demographic data from patient and medical record	6	12 August 2011
Other: Substantial amendment form		17 October 2011
Other: Email from Dr Anderson		11 October 2011
Other: Letter from Dr Anderson		11 October 2011
Other: Letter of indemnity		31 March 2011
Other: Letter of insurance policy		28 March 2011
Participant Consent Form: Patient	6	12 August 2011
Participant Consent Form: Carer	6	12 August 2011
Participant Consent Form: Healthcare professional	6	12 August 2011
Participant Information Sheet: Carer	6	12 August 2011

Participant Information Sheet: Health Care Professional (Interview)	8.0	14 November 2011
Participant Information Sheet: Patient	8.0	14 November 2011
Participant Information Sheet: Health Care Professional (Focus Group)	8.0	14 November 2011
Protocol	8.0	14 November 2011
REC application		15 August 2011
Response to Request for Further Information		14 November 2011
Summary/Synopsis	6	12 August 2011

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document *"After ethical review – guidance for researchers"* gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

Feedback

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

Further information is available at National Research Ethics Service website > After Review

11/YH/0344	**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project

Yours sincerely

Dr Carol Chu
Chair

Email: jade.thorpe@nhs.net

Copy to: *Ms Emma Calverley*
Mr James Illingworth, Hull And East Yorkshire Hospitals NHS Trust

Appendix 9 Participant information sheets

9.1 Participant information sheet: Patient

PARTICIPANT INFORMATION LEAFLET: PATIENT

Title of study: Views of patients and carers when heart failure becomes more severe

We should like to invite you to consider taking part in our research study. Before you decide, you need to understand why the research is being done and what it would involve for you.
Talk to other people, such as your family, friends or doctor about the study if you wish.
If you have any questions, please feel free to contact us.
Thank you for taking the time to read this.

Why is the study being done?

There is a lot of variety in the symptoms, experiences and care for patients with heart failure as their disease becomes more severe. We know that some patients and their families have difficulties at this time. It is thought that an approach that includes focusing on quality of life and helping symptoms may be beneficial. We would like to know how this approach to your care has been managed, and your views on this- both

good and bad.We can use this information to try and improve the care for patients and their carers by better understanding what has helped and what is still difficult.

Why have I been asked to consider taking part?

You have been identified by one of the doctors or nurses looking after you because you have been living with heart failure for some time, and have experienced further problems over the last few months. You will have had a conversation or a number of conversations with a doctor or nurse about understanding that cure or full control of your symptoms is unlikely to be possible and changing the focus of your care to helping minimise the impact of your symptoms and offering more support to you and your family.

Do I have to take part in this study?

It is up to you to decide whether or not you wish to join this study.
If you decide not to take part, you do not need to give a reason, nor will your decision affect your treatment in any way.

If you do agree to take part, we shall ask you to sign a consent form. You are free to withdraw at any time, without giving a reason. This will not affect the standard of care you receive.

Upon agreement to take part in the study, one of the research team will describe the procedure and go through this information leaflet with you No one need know, not even the person who suggested you, whether or not you have decided to take part in the study.

What will happen if I decided to take part in the study

One of the research team, Amy Gadoud will contact you to arrange a time to come to your home and meet with you. She can meet at another place if you prefer. The study will involve being asked questions about your experience of heart failure, how it affects you and how you are looked after by health care professionals. Amy is particularly interested in finding out if the management of your disease has changed and your views on this, both good and bad. The interview should take about thirty to forty minutes, but no more than one hour. The interview will be audio-recorded, and you may stop the interview at any time without giving a reason.

If you would like you could have a family member or friend with you during the interview to support you. They would not be participating in the study. They would also be able to stop the interview at any point. We would stop the recording and you would be able to talk with this person. You would then make a decision if you wished to carry on with the interview or stop it. Their role is to support you, but is your decision if you wish to continue with the interview or not.

Amy will also like to talk to the person you feel is closest to you in terms of day-to-day care. If you agree to take part in this study, she will ask you to let the person closest you know about the study and check whether they are happy to be contacted. Amy will also like to speak to the health care professional(s) you feel is/are most involved in your healthcare. She will contact them for you.

The research team would also like to access your medical notes to collect further information.

What are the possible disadvantages of taking part in the study?

You will be talking about your illness in some detail. Some people find it upsetting to talk about their illness, how it affects them now, and the affects it may have in the future. If this is your experience, you may ask the researcher to move on to another topic, or stop the interview altogether.

What are the possible advantages of taking part in the study?

Some people may find talking about their illness helpful. However, there is no specific advantage to your to taking part in this study. We are carrying it out to see if we can help the care of patients with severe heart failure in the future.

What if there is a problem?

If you have a concern about any aspect of this study, you may to speak to the researchers who will do their best to answer your questions. If you remain unhappy and wish to complain formally, you may do this through the normal National Health Service complaints procedure or Patient Advice and Liaison Service (PALS). If you would like to talk to other patients and carers who have experience of medical research, you may contact the North and East Yorkshire and Northern Lincolnshire Consumer Research Panel. All the contact details are at the end of this leaflet.

In the unlikely event something should go wrong and you are harmed during the research due to someone's negligence, then you may have grounds for a legal action for compensation against the University of Hull, but you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you.

Will my taking part in the study be kept confidential?

Everything you tell us will be strictly confidential. Any information held on computer will be password protected and all audio-recordings and written notes will be stored securely in locked filing cabinets in the Research Department. The information will only be available to the research team and transcripts will be anonymised. The files will be destroyed five years after the study is complete. Anonymised information will be archived and may be used in future research.

We may use quotes from your interview, but we will ensure that any identifying information will be removed.

If something very serious was discovered during the course of research i.e. abuse or neglect, then the research team have a duty of care to report this to the appropriate agencies.

Involvement of your General Practitioner (GP)/ Family doctor

With your permission, we shall let your GP know that you are in the study as he/she may find that information helpful. It will not affect your medical care in any way.

What will happen to the results of the research study?

The intention is to write up this research as part of a PhD (researchdegree). We also intend to write up our work in reports and papers for medical journals and conferences. We should like to assure you that your experiences and opinions will not be identifiable in any of our publications, and your information will be combined with that of other patients' so that you will not be identified in any way. In addition, your doctors and nurses will not know what you have said to us.

Who is organising and funding the research?

The salary of the main researcher is paid by HullYorkMedicalSchool. Other research costs are paid from Dr Miriam Johnson's research fund. There is no commercial sponsorship of this study.

Who has reviewed the study?

All research in the NHS is looked at by independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and given favourable opinion by Leeds East Research Ethics Committee.
The North and East Yorkshire and Northern Lincolnshire Consumer research panel have also reviewed this study. This is an independent group of patients and carers who have an interest in research.

Further information and contact details

This study is being carried out by researchers from HullYorkMedicalSchool. The research team are:

- Amy Gadoud who is a Clinical Fellow at Hull York Medical School; Tel 07816926167; email amy.gadoud@hyms.ac.uk
- Miriam Johnson who is a Consultant at St Catherine's Hospice, Scarborough and a Reader in Palliative Medicine at Hull York Medical School; email Miriam.johnson@hyms.ac.uk

- Una Macleod who is a GP in Hull and Professor of Primary Care at Hull York Medical School; tel 01482 463074

You will be able to find out more about the study by contacting the researchers above.

Other contacts:

- The North and East Yorkshire and Northern Lincolnshire Consumer Research Panel; tel 01482 476680; email jane.ash@nhs.net.
- Patient Advice and Liaison Service (PALS)
  York Teaching Hospital NHS Foundation Trust, Freepost, NEA 11112, York, YO30 7ZZ.
  pals@york.nhs.uk
  01904 726262

If you do decide to take part in the study you will be given a signed copy of your consent form.

Thank you very much for considering taking part in our research. Please discuss this information with your friends, family or doctor if you wish.

Expression of Interest Form: Views of patients and carers when heart failure becomes more severe

H·Y·M·S
THE HULL YORK MEDICAL SCHOOL

Please cross one of the following boxes and return in the stamped addressed envelope

No, I do not want to hear more about the study ☐

Yes, I am willing to consider taking part in the study ☐

If **yes,** would you prefer to receive more information by a telephone call from one of the researchers, or would you prefer for Amy Gadoud, the study researcher, to contact you to arrange a visit?

Telephone call from researcher ☐

Call to arrange a visit ☐

Best times to call……

Signature ……

Name (print) ……..

Date ……..

Tel number ……

9.2 Participant information sheets: Carers

PARTICIPANT INFORMATION LEAFLET: CARER

Title of study: Views of patients and carers when heart failure becomes more severe

We should like to invite you to consider taking part in our research study. Before you decide, you need to understand why the research is being done and what it would involve for you.
Talk to other people, such as your family, friends or doctor about the study if you wish.
If you have any questions, please feel free to contact us. Thank you for taking the time to read this.

Why is the study being done?

There is a lot of variety in the symptoms, experiences and care for patients with heart failure as their disease becomes more severe. We know that some patients and their families have difficulties at this time. We particularly interested in finding out if the way your

relative or friend's condition has been managed has changed in any way, and your views on this- both good and bad. We can use this information to try and improve the care for patients and their carers by better understanding what has helped and what is still difficult.

Why have I been asked to take part?

You have been identified by your relative or friend as the person they feel is closest to them in terms of their day to day care. Your relative or friend is someone who has been living with heart failure for some time but has experienced more problems over the last few months.

Do I have to take part?

It is up to you to decide whether or not you wish to join this study.

If you decide not to take part, you do not need to give a reason nor will your decision affect your relative or friend's treatment in any way.

If you do agree to take part, we shall ask you to sign a consent form. You are free to withdraw at any time, without giving a reason. This would not affect the standard of care your relative or friend receives.

Upon agreement to take part in the study, a member of the research team will describe the procedure and go through this information leaflet with you.

No one need know, not even the person who suggested you, whether or not you have decided to take part in the study.

What will happen if I decided to take part in the study?

One of the research team, Amy Gadoud would contact you to arrange a time to come to your house and meet you. We could meet at another place if you preferred. The study would involve being asked questions about being the carer of someone with heart failure and how you are looked after by health care professionals. Amy is particularly interested in finding out if the management of your relative or friend's disease has changed and your views on this, both good and bad. The interview should take about thirty to forty minutes but no more than one hour. The interview would be audio- recorded, and you may stop the interview at any time without giving a reason.

What are the possible disadvantages of taking part in the study?

You will be talking about your relative or friend's illness in some detail. Some people might find it upsetting to talk about this, how it affects them now, and the affects it may have in the future. If this is your experience, you may ask the researcher to move on to another topic, or stop the interview altogether.

What are the possible advantages of taking part in the study?

Some people may find talking about their relative or friend's illness helpful. However, there is no specific advantage to you to taking part in this study. We are carrying it out to see if we can help the care of patients with severe heart failure in the future.

What if there is a problem?

If you have a concern about any aspect of this study, you may to speak to the researchers who will do their best to answer your questions. If you remain unhappy and wish to complain formally, you may do this through the normal National Health Service complaints procedure or Patient Advice and Liaison Service (PALS). If you would like to talk to other patients and carers who have experience of medical research, you may contact the North and East Yorkshire and Northern Lincolnshire Consumer Research Panel. All the contact details are at the end of this leaflet.

In the unlikely event something should go wrong and you are harmed during the research due to someone's negligence, then you may have grounds for a legal action for compensation against the University of Hull, but you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you.

Will my taking part in the study be kept confidential?

Everything you tell us will be strictly confidential. Any information held on computer will be password protected and all audio-recordings and written notes will be stored securely in locked filing cabinets in the Research Department. The information will only be available to the research team and transcripts will be anonymised. The files will be destroyed five years after the study is complete. Anonymised information will be archived and may be used in future research.

We may use quotes from your interview, but we will ensure that any identifying information will be removed.

If something very serious was discovered during the course of research i.e. abuse or neglect, then the research team have a duty of care to report this to the appropriate agencies.

What will happen to the results of the research study?

The intention is to write up this research as part of a PhD (research degree). We also intend to write up our work in reports and papers for medical journals and conferences. We should like to assure you that your experiences and opinions will not be identifiable in any of our publications, and your information will be combined with that of other carers' so that you will not be identified in any way. In addition, your relative or friend's doctors and nurses will not know what you have said to us.

Who is organising and funding the research?

The salary of the main researcher is paid by Hull York Medical School. Other research costs are paid from Dr Miriam Johnson's research fund.
There is no commercial sponsorship of this study.

Who has reviewed the study?

All research in the NHS is looked at by independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and given favourable opinion by Leeds East Research Ethics Committee. The North and East Yorkshire and Northern Lincolnshire Consumer research

panel have also reviewed this study. This is an independent group of patients and carers who have an interest in research.

Further information and contact details

This study is being carried out by researchers from Hull York Medical School. The research team are:

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- Miriam Johnson who is a Consultant at St Catherine's Hospice, Scarborough and a Reader in Palliative Medicine at Hull York Medical School; email Miriam.johnson@hyms.ac.uk
- Una Macleod who is a GP in Hull and Professor of Primary Care at Hull York Medical School; tel 01482 463074

You will be able to find out more about the study by contacting the researchers above.

Other contacts:

- The North and East Yorkshire and Northern Lincolnshire Consumer Research Panel; tel 01482 476680; email jane.ash@nhs.net.
  Patient Advice and Liaison Service (PALS), York Teaching Hospital NHS Foundation Trust, Freepost, NEA 11112, York, YO30 7ZZ.
  pals@york.nhs.uk
  01904 726262

If you do decide to take part in the study you will be given a signed copy of your consent form.

Thank you very much for considering taking part in our research. Please discuss this information with your friends, family or doctor if you wish.

Expression of Interest Form: Views of patients and carers when heart failure becomes more severe

H·Y·M·S
THE HULL YORK MEDICAL SCHOOL

Please cross one of the following boxes and return in the stamped addressed envelope

No, I do not want to hear more about the study ☐

Yes, I am willing to consider taking part in the study ☐

If **yes,** would you prefer to receive more information by a telephone call from one of the researchers, or would you prefer for Amy Gadoud, the study researcher, to contact you to arrange a visit?

Telephone call from researcher ☐

Call to arrange a visit ☐

Best times to call……

Signature ……

Name (print) ……..

Date ……..

Tel number ……..

12th August 2011
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9.3 Patient information sheets: Health care professionals

H·Y·M·S
THE HULL YORK MEDICAL SCHOOL

PARTICIPANT INFORMATION LEAFLET: HEALTH CARE PROFESSIONAL (INTERVIEW)

Title of study: Views of patients and carers when heart failure becomes more severe

We should like to invite to consider taking part in our research study. If you would like some more information, please feel free to contact us. Thank you for taking the time to read this.

Why is the study being done?

There is a lot of variety in the symptoms, experiences and care for patients with heart failure as their disease becomes more severe. We know that some patients and their families have difficulties at this time. It is thought that an approach that recognises that cure or full control of symptoms is unlikely to be possible and changing the focus of care to minimising the impact of symptoms and offering more support to the patient and their family may be beneficial. This study has interviewed patients who have experienced this change in order to better understanding what has helped and what is still difficult.

Why have I been asked to take part?

You have been identified by the patient as the health care professional most involved in their care.

Do I have to take part?

It is up to you to decide to join the study. If you agree to take part, we will ask you to sign a consent form. You are free to withdraw at any time, without giving a reason. This would not affect your employment in any way.

What will happen if I decided to take part in the study

One of the research team, Amy Gadoud would contact you to arrange a convenient time and place for the interview and it can take place on the telephone if you prefer. Amy would ask you about the change in focus of care for that particular patient and more generally. The interview would take about thirty to forty minutes. The interview would be audio- recorded.

What are the possible advantages or disadvantages of taking part in the study?

You may find it helpful to reflect on the care of patients with severe heart failure but there is no specific advantage to you to taking part in this study. We are doing it to see if we can help the care of patients with heart failure in the future.

What if there is a problem?

If you have a concern about any aspect of this study, you may to speak to the researchers who will do their best to answer your questions. If you remain unhappy and wish to complain formally, you may do this through the normal National Health Service complaints procedure or Patient Advice and Liaison Service (PALS). If you would like to talk to other patients and carers who have experience of medical research, you may contact the North and East Yorkshire and Northern Lincolnshire Consumer Research Panel. All the contact details are at the end of this leaflet.

In the unlikely event something should go wrong and you are harmed during the research due to someone's negligence, then you may have grounds for a legal action for compensation against the University of Hull, but you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you.

Will my taking part in the study be kept confidential?

Everything you tell us will be strictly confidential. Any information held on computer will be password protected

and all audio-recordings and written notes will be stored securely in locked filing cabinets in the Research Department. The information will only be available to the research team and transcripts will be anonymised. The files will be destroyed five years after the study is complete. Anonymised information will be archived and may be used in future research.

We may use quotes from your interview, but we will ensure that any identifying information will be removed.

If something very serious was discovered during the course of research i.e. abuse or neglect, then the research team have a duty of care to report this to the appropriate agencies.

What will happen to the results of the research study?

The intention is to write up this research as part of a PhD. We also intend to write up our work in reports and papers for medical journals and conferences. We would like to assure you that your experiences and opinions will not be traceable back to you in any of our publications, and your information will be combined with that of other professionals' so that you will not be identified in any way.

Who is organising and funding the research?

The salary of the main researcher is paid by Hull York Medical School. Other research costs are paid from D r Miriam Johnson's research fund. There is no commercial sponsorship of this study.

Who has reviewed the study?

All research in the NHS is looked at by independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and given favourable opinion by Leeds East Research Ethics Committee. The North and East Yorkshire and Northern Lincolnshire Consumer research panel have also reviewed this study. This is an independent group of patients and carers who have an interest in research.

Further information and contact details

This study is being carried out by researchers from Hull York Medical School. The research team are:

- Amy Gadoud who is a Clinical Fellow at Hull York Medical School; Tel 07816926167; email amy.gadoud@hyms.ac.uk
- Miriam Johnson who is a Consultant at St Catherine's Hospice, Scarborough and a Reader in Palliative Medicine at Hull York Medical School; email Miriam.johnson@hyms.ac.uk
- Una Macleod who is a GP in Hull and Professor of Primary Care at Hull York Medical School; tel 01482 463074

You will be able to find out more about the study by contacting the researchers above.

Other contacts:

- The North and East Yorkshire and Northern Lincolnshire Consumer Research Panel; tel 01482 476680; email jane.ash@nhs.net.
- Patient Advice and Liaison Service (PALS)
  York Teaching Hospital NHS Foundation Trust, Freepost, NEA 11112, York, YO30 7ZZ.
  pals@york.nhs.uk
  01904 726262

If you do decide to take part in the study you will be given a signed copy of your consent form.

Thank you very much for considering taking part in our research.

Appendix 10 Topic Guides

10.1 Topic guide: semi-structured interview: patient

General information about condition

What do you understand about your condition?

Can you tell me about information you have been given about your condition?

Tell me about how that information was given? Do you have enough information? Could you ask for more information if you wanted to?

Who is involved in your care, family/ friends which health care workers?

Transition

Have you noticed a change in your condition over the last few weeks to months?

If more poorly - how have you come to that conclusion? If feeling better, why?

If unable to tell, how do you feel compared to a year ago etc..?

More poorly? More symptoms? More visits to hospital?

What has the effect of this been for you and your family?

Do you feel the care you receive from the doctors and nurses has changed recently?

Communication

Have you talked to anyone about this?

If yes explore who, who started the conversation(s) was it helpful? Distressing? Anything not discussed that would have liked to etc…?

If no, would you like to, with whom? Home or hospital? Would you bring up the topic yourself?

Impact

What are the difficulties about living with your condition?

What people/services do you find particularly helpful?

What else would help?

Do you feel helpless/ overwhelmed at times?

What would help at these times? Has anything been suggested?

Are your needs addressed?

How do you see the future?

How do you see the next few weeks / months going?

Do you talk to anyone about this? Friends family, healthcare workers? Would you like to?

Conclusion

Advice to others in a similar situation?

Anything else about your experiences you would like to share with me?

10.2 Topic guide: semi-structured interview: carer

General information

How would you describe your relationship with X? Husband /Wife/ Daughter/ friend? Carer?

Tell me what it is like for you caring for X?

What do you understand about X's condition?

Do you have enough information about X's condition?

How does it work for you getting information about X condition? Could you ask for more information if you wanted to?

Who else is involved in X care, family/ friends, which healthcare workers?

Transition

Have you noticed a change in X's condition over the last few weeks to months?

If more poorly - how have you come to that conclusion? If feeling better, why?

If unable to tell, compare to how he/she was a year ago etc..?

More poorly? More symptoms? More visits to hospital?

What has the effect of this been for you and X?

Do you feel the care X receives from the doctors and nurses has changed recently?

If you feel X care has changed recently, what do you feel your role has been in making that change happen?

Communication

Have you talked to anyone about this?

If yes explore who, who initiated conversation was it helpful? Distressing? Anything not discussed that would have liked to etc…?

If no, would you like to, with whom? Home or hospital? Would you bring up the topic yourself?

How do you feel when talking with the doctors and nurses about X?

How confident? Has this changed? Do you feel your thoughts are taken into account?

Impact

What are the difficulties for X with living with his condition? And for you?

What people/services do you/X find particularly helpful?

What else would help?

Does X feel helpless/ overwhelmed at times? Do you?

What would help at these times? Has anything been suggested?

Are your needs addressed?

How do you see the future?

How do you see the next few weeks / months going?

Do you talk to anyone about this? X other family members, healthcare workers? Would you like to?

Conclusion

Advice to others in a similar situation?

Anything else about your experiences you would like to share with me?

10.3 Topic guide: semi-structured interview: Health care professional

General information

Tell me about Mr/Mrs X care?

Transition

Tell me about the focus of Mr/Mrs X care over the last few weeks to months?

Do you feel there has been a change in focus to a more palliative management? If so, how did this happen?

If not explore reasons why not?

What is the effect of the transition for X and his or her family?

What do you think X understanding of the change in focus is?

Any remaining concerns or issues that you, X or their family have?

What helped the transition?

What were the roles of other professionals? Helpful or not?

What do you think of the concept of transition/ change to a palliative care approach in heart failure? Is it helpful?

Communication

What do you think about having a conversation with X that their disease is more advanced?

Have you or anyone else had such conversations? Who started the conversation? What was discussed? If not explore why not?

What about advance care planning / preferred place of care / unscheduled admission to hospital / end of life care?

What do you think X understands about the management of his or her condition?

What about the palliative care register (Gold Standards Framework) for X?

Recognising advanced disease

Have you thought about X's prognosis? Do you think he/she has?

Has prognosis affected how you manage X?

What are the triggers for you for thinking of a palliative care approach in advanced heart failure? What were the triggers for X?

For both communication and recognising advanced disease: what were the problems/ difficulties?

What would be helpful in these situation for you? For the patient? For their carer?

Conclusions

Do you think X and his or her management are typical example of the patients you look after with heart failure?

Are you pleased with X management?

Anything you would highlight to others as something that worked well?

Is there anything you would have done differently?

Specific questions that has arose interview with X

Could ask some focus group questions

Glossary

Abbreviation	Term in full
ACEI	Angiotensin Converting Enzyme Inhibitors
ACP	Advance care planning
ADA	After Death Analysis
AIDS	Acquired Immunodeficiency Syndrome
BMI	Body Mass Index
BNF	British National Formulary
BP	Blood Pressure
CI	Confidence Interval
CKD	Chronic Kidney Disease
CPRD	Clinical Practice Research Datalink
COPD	Chronic Obstructive Pulmonary Disease
DNAR	Do not attempt resuscitation
DM	Diabetes mellitus
DS1500	Form completed by clinician to allow fast track to certain benefits if poor prognosis
DVD	Digital Versatile Disk
EF	Ejection Fraction
EFFECT-HF score	Enhanced Feedback for Effective Cardiac Treatment-Heart Failure score (prediction score to stratify the risk of death in heart failure patients)
EMIS	Egton Medical Information Systems
GCP	Good Clinical Practice
GPRD	General Practice Research Database
GMC	General Medical Council
GP	General Practitioner/ General Practice
GSF	Gold Standards Framework
HCP	Health care professionals
HF	Heart Failure
HFNS	Heart Failure Nurse Specialists
HF-PEF	Heart Failure with Preserved Ejection Fraction
HR	Hazard Ratio
ICD	Implantable cardioverter-defibrillator
ISAC	Independent Scientific Advisory Committee
NHS	National Health Service
NICE	National Institute for Clinical Excellence /National Institute for Health and Care Excellence
NRES	National Research Ethics Service
NT-proBNP	N Terminal Pro Brain Natriuretic Hormone
NYHA	New York Heart Association (classification of heart failure based on severity of symptoms I-IV)
MHRA	Medicines and healthcare products regulatory agency
MRC	Medical Research Council
MREC	Multi centre research ethics committee
NIHR	National Institute for Health Research

Abbreviation	Term in full
ODBC	Open Data Connectivity
OPD	Outpatient department
PCT	Primary Care Trust
PPC	preferred priorities for care
QOF	Quality and Outcomes Framework
QOL	Quality of Life
RCT	randomised controlled trial
REC	Research Ethics committee
RVEF	Right Ventricular Ejection Fraction
SD	Standard deviation
SHFM	Seattle Heart Failure Model
SPCP	specialist palliative care professional
SPICT	Supportive and Palliative Care Indicators Tool
UK	United Kingdom
US	United States
UTS	Up to standard, term used by GPRD when quality assessed data
WHO	World Health Organisation