School of Nursing and Midwifery

An integrated approach to outcome evaluation: Incorporating Patient Reported Outcomes in Heart Failure

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Declaration

To the best of my knowledge and belief this thesis contains no material previously published by any other person except where due acknowledgement has been made.

This thesis contains no material which has been accepted for the award of any other degree or diploma in any university.

Sungwon Chang

4th July 2013

Date

Acknowledgement

I started my PhD journey because I was afraid. Afraid of not being “good enough” and “smart enough”. I felt like a fraud most of the time as an academic. To me PhD was not just a journey to become an independent researcher but a path to self-discovery and a different way to see the world. At the start of my PhD, I was asked by the Dean of my school at University of Western Sydney, how I saw myself at the end of my PhD and I told him I see myself as not being afraid and now I believe I am getting there.

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Anthology of publications and presentations associated with this thesis

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Abstract

Globally individuals and health care systems are facing the burden of chronic illness. The impact of the increasing burden of non-communicable diseases is experienced by individuals and health care systems. Across the globe health care systems are struggling to meet the increasing demands for services within the confines of rising costs and needs for accountability. Beyond costs and treatment allocations, there is an increasing mandate to provide care that is patient centred and appropriate to the needs of the individual. The Innovative Care in Chronic Condition (ICCC) framework has been successful in driving health care reforms to meet the needs of individuals with chronic illness internationally. Deriving metrics that allow monitoring of conditions at the level of the patient, provider and health care system are of increasing importance. Comprising this thesis is a series of studies to investigate outcomes that includes the patient's perspective in the evaluation of clinical interventions. To achieve this, chronic heart failure, was used as an exemplar of a chronic condition.

Chronic heart failure (CHF) is the final common pathway for many cardiac conditions. As a consequence has emerged as a major public health problem and represents as an excellent exemplar of living with a chronic illness. CHF patients commonly experience high levels of ill-health, disability and mortality placing a heavy burden on health care systems. Hospitalisations are frequent and costly to both CHF patients and to society. People with CHF live with a limited quality of life and physical ability and the prognosis for CHF is poor. Given the nature of debilitating symptoms, and their potential impact on physical, social and psychological aspects of life, patient's perspective in outcome assessment is essential in providing effective care.

Specifically this study sought to:

- Examine patient reported outcomes in clinical management and in clinical research
- Investigate patient important outcomes, their utility, relevance and acceptability amongst patients, clinicians, researchers and administrators

- Test composite outcomes model that integrate patient important outcomes in clinical trials research

Patient reported outcomes (PROs) is a strategy to capture the patient perspective and experience on their health status. The use of PROs can be incorporated in clinical assessments, monitoring of clinical progress as well as clinical research. Despite their frequent use in research, evidence suggests that to date they have had a limited influence on clinical practice and policy. As part of this thesis an integrative review was conducted to explore the potential utility of PROs at the policy level. By using the ICCC framework, PROs were indeed essential to improve the management of CHF at the micro, meso and macro levels of decision making.

One of the key challenges in using PROs and outcomes important to individuals in CHF is limited methodological and reporting quality. This is cited as a reason why many clinicians are sceptical of the utility of PROs. To explore issues in reporting a review was conducted on RCTs of pharmacological therapy in CHF that reported health related quality of life (HRQoL) as a primary or secondary outcome. Using the *Minimum Standard Checklist* for evaluating the quality of reporting of HRQoL outcomes resulted in 26 (19.1%) studies being considered 'very limited' in terms of methodological and reporting rigour, and 91 (66.9%) were evaluated as 'limited' and only 19 (14.0%) studies were considered to be of a 'probably robust' quality. In fact, the quality of HRQoL reporting has not improved over time. Some of the issues identified are limited discussions, methodological shortcomings, and poor HRQoL reporting. This review has underscored the importance of standardising of the reporting of HRQoL measures.

Although capturing the patient's perspective via PROs is important, they may not be the only outcome measures important to patients. Currently, no single CHF outcome measure captures all dimensions of the quality of care from the patient's perspective. To identify outcome measures in CHF deemed important to patients, a structured literature review was undertaken. The conceptual and methodological challenges and opportunities in each outcome measure were identified as important to patients with CHF. That is mortality, hospitalisation and PROs were

identified as important to patients but also meaningful and relevant to the provider and health care system as well. These outcome measures were proposed as a core outcome set that represent the minimum set of outcomes that should be measured and reported in CHF.

A number of composite outcome measures have been developed to capture the perspective of the patient, clinician as well as including objective measures of health. Three validated composite outcomes, the Packer's Score, Cleland's Patient Journey and the composite endpoint used in the African American Heart Failure Trial (A-HeFT) were examined in a secondary analysis of a prospective, multi-center randomized controlled trial of 280 hospitalized CHF patients in the Which Heart failure Intervention is most Cost-effective & Consumer Friendly in Reducing Hospital Care (WHICH?) Trial in order to assess the comparability and interpretability of the measures in a pragmatic clinical trial. Correlation coefficients demonstrated substantial associations amongst all three composite endpoints. Although there was a considerable agreement across the three measures when estimating deteriorating condition, these was less when estimating improvements.

This thesis has described both the importance and complexity of including outcome measures that are meaningful to patients in both the assessment of individuals' needs, testing interventions, monitoring outcomes and assessing process and outcome measures at a health systems level. This thesis has also extended the discussion and debate around PROs to discuss Patient Important Outcomes, which is outcomes that patients notice and for which they would be willing to undergo a treatment with associated risk, cost, or inconvenience for it to be the only thing that changed. Using CHF as an exemplar has provided useful insights into the dimensions and complexities of measuring outcomes in chronic and complex conditions. As the burden of chronic disease continues to increase refining the metrics of outcome measurements will be equally as important as refining novel therapies. This will be critical to develop and implement interventions to meet the growing numbers of people living with chronic illness.

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Abbreviations

Abbreviation	Full term
A-HeFT	African American Heart Failure Trial
CBI	Clinical based intervention
CHF	Chronic Heart Failure
CONSORT	Consolidated Standard of Reporting
DAOH	Days Alive and Out of Hospital
EQ-5D	European Quality of Life Instrument – 5 Dimensions
FDA	Food and Drug Administration
HBI	Home based intervention
HF	Heart Failure
HRQoL	Health Related Quality of Life
ICCC	The Innovative Care for Chronic Condition
IQR	Interquartile Range
M	Mean
Md	Median
MeSH	Medical Subject Heading
MID	Minimal Important Difference
MLWHF	Minnesota Living With Heart Failure Questionnaire
MSC	Minimum Standard Checklist
NCD	Non Communicable Disease
NHS	National Health
NYHA	New York Heart Association

PCORI	Patient Centred Outcomes Research Institute
PIO	Patient Important Outcome
PROMs	Patient Reported Outcomes Measures
PROs	Patient Reported Outcomes
QALY	Quality Adjusted Life Years
QoL	Quality of Life
RCT	Randomised control trials
SD	Standard deviation
US	United States
WHICH (?)	Which Heart failure Intervention is most Cost-effective & Consumer Friendly in Reducing Hospital Care?

Chapter 1 Introduction

1.1 Introduction

Globally people are living longer with multiple chronic illnesses. This is occurring as a consequence of increased longevity and improved medical care options. This epidemiological transition from infectious to chronic diseases is placing an overwhelming demand on contemporary society [1]. These changes in epidemiology and management of disease not only challenge treatment allocation but also measures of efficacy and effectiveness of health interventions [2]. Currently, existing metrics of evaluation at the level of the patient, health care provider and health care system are inadequate to meet this challenge [3].

In managing chronic conditions, there is a need to capture the unique perspective of the patient in clinical and therapeutic interactions and to derive outcomes that are meaningful to patients, clinicians and policy makers [4]. This is critical not only in the assessment and planning of clinical care but also in obtaining useful and relevant outcome measures that reflect the patient's view [4] to promote patient centred care. Patient centred care is defined as "care that is respectful of and responsive to individual patient preferences, needs, and values and ensures that patient values guide all clinical decisions" [5, p3]. The focus is the patient rather than the disease or condition and the priority is no longer the treatment but the patient and the individual's particular health needs [6].

This thesis investigated outcomes in chronic conditions, using chronic heart failure (CHF) as an exemplar; and tested a comprehensive evaluation model from the perspective of an organisation, providers and consumers, incorporating patient reported outcomes (PROs) that are meaningful and relevant to patients, their families, clinicians and policy makers.

As an introduction, this chapter provides the background to the study, problem statement, and study aims. Specifically this chapter discusses the burden of CHF and outcome measures important to patients in CHF. It proceeds to explore the need for outcomes from patients, providers and system perspectives and discusses the need for a more comprehensive approach to outcome assessment that focuses on the patients' perspective. The chapter concludes with an overview of the thesis.

1.2 Problem statement and rationale

Measuring outcomes as an indicator of patient care has been an important driver of contemporary healthcare systems [7]. The ageing population and an epidemiological shift from acute to chronic conditions have posed an overwhelming demand for healthcare infrastructure [1]. This transition has also redefined the needs and expectations of healthcare with much of the responsibilities for the care falling on the patients and their families [8]. When chronic conditions reach the advanced stages, the primary treatment goal is no longer quantity but quality of life [9]. Consequently to measure the effectiveness of healthcare comprehensively, the traditional outcome measures of health such as mortality and morbidity are seen to be increasingly inadequate[10].

Incorporating the perspectives and preferences of patients about their treatment is becoming prominent in setting goals of medical care [9]. Moreover, as complexity, burden, and cost of treatment escalate, it is vital that patients and their families, clinicians, policy makers and funding bodies have realistic expectations of physical as well as psychological and social outcomes [11]. Such expectations are contingent on strategies to measure these constructs by means that are reliable, valid, relevant, acceptable and have utility amongst patients, clinicians, researchers and administrators.

1.3 Chronic heart failure

CHF is a disabling and progressive condition and is the final pathway of most heart diseases. The National Heart Foundation/Cardiac Society of Australia and New Zealand defines CHF as a:

" ..complex clinical syndrome with typical symptoms (e.g. dyspnoea, fatigue) that can occur at rest or on effort, and is characterised by objective evidence of an underlying structural abnormality or cardiac dysfunction that impairs the ability of the ventricle to fill with or eject blood (particularly during physical activity). A diagnosis of CHF may be further strengthened by improvement in symptoms in response to treatment." [12]

The unpredictability and severity of physical symptoms such as dyspnoea, fatigue and oedema has led to adverse health outcomes and distress for patients living with CHF [13]. Numerous studies have also shown that CHF is associated with depression, and that this association is linked with a worse prognosis [14]. In studies with comparative normative data the degree of physical, mental and social functioning impairment was greater in CHF patients than other chronic diseases sufferers [15, 16]. In fact, many patients with advanced CHF ascribe greater importance to quality than to duration of life which may be limited by CHF [9]. Furthermore, CHF is the leading cause of hospitalisation in industrialised countries [17] with high re-admission rates [18] and prolonged length of stay which all lead to an increasing burden on resources both personally for patients, and financially for health care services [19]. In developed countries CHF accounts for 1% to 2% of all healthcare expenditure [20].

1.3.1 Burden of chronic heart failure

CHF is primarily a condition of ageing. As treatment of hypertension, acute myocardial infarction and valvular disorders have met with increasing success, the incidence and prevalence of CHF has increased dramatically. The prevalence of CHF has been shown to increase from less than 1% in the 20-39 years to over 20% in 80 years and older [21]. In addition the incidence of CHF doubles between 65-74 years and 75-84 age bands [22]. Increasingly, ethical and treatment conundrums arise out of the need to accurately assess the wishes of patients and their families and further tailor services to meet the needs of the vulnerable elderly. [23, 24]

Despite the progress in the treatment of CHF, the prognosis for people with CHF remains poor, with a five-year mortality rate in excess of 50% and ongoing symptomatic limitation [25]. Based on a 44-year follow up of the Framingham study and 20 year follow up of the offspring cohort, 80% of men and 70% of women under the age of 65 years living with CHF die within eight years [21], 30-day mortality was around 10%, the one-year mortality rate after CHF diagnosis was 20-30%, and five year mortality was 45-60%[21]. The lifetime risk of developing heart failure is one in five [26].

Patients living with CHF experience a range of symptoms [27], with the majority of CHF patients experiencing multiple symptoms concurrently [28, 29]. The most common and debilitating symptoms are breathlessness, fatigue [28-31], and oedema [27, 29]. Breathlessness and fatigue may impact on social aspects of people's lives [32], and may also cause psychological distress and depression [31]. Other symptoms of CHF include insomnia [33, 34], pain [28, 30, 31], palpitations, coughing, dizziness [29], and low exercise tolerance [35]. As the illness trajectory for CHF is progressive, irreversible and inevitably fatal [36], treatment goals seek to prolong life, minimize symptoms and to avoid unpleasant events such as hospitalization [37] in a culturally appropriate and cost-effective manner.

Every year, in Australia alone, more than 30,000 are estimated to be diagnosed with CHF[38] and AU$1000 million of the health-care budget is expended on this condition annually [39]. Furthermore, with an ageing population surviving longer with the burden of chronic diseases, the expenditure of funds and health care expenditure within the elderly age group rises [38].

Hospitalisations for individuals with CHF are frequent and costly to individuals with CHF [40]. People with CHF live with limited quality of life [41] and physical ability [41] and the prognosis for CHF is poor [42]. Given the nature of debilitating symptoms, and their potential impact on physical, social and psychological aspects of life, assessing outcomes important to patients is essential in providing effective care.

1.3.2 Chronic heart failure and evidence based practice

A diagnosis of CHF presents challenges in caring for the elderly with a chronic condition from the perspective of the individual with the condition, their family and carers, as well as health professionals and the systems to support them [43]. Namely, it is a recurrent, costly and resource intensive chronic condition with an illness trajectory punctuated by episodes of decompensation and poor prognosis [42]. In spite of extensive evidence, there is evidence of a treatment gap that necessitates researchers, clinicians, administrators and policy makers to collaborate on strategies to achieve an evidence-based approach to health care [44]. Equally,

we are aware that some treatments may impact adversely on patients' perception of quality of life (QoL) in spite of improving more traditional outcomes such as mortality [45] . It is important to remember that the definition of evidence-based health care relates not only to the best practice treatments, but also to the administration of these in accordance with the patient's values and preferences and clinician expertise [46]. Although substantive literature exists in discrete categories, such as QoL and health service evaluation, there is considerably less experience in the integration and the synthesis of this information to provide an outcome measurement model that takes into consideration clinical, organizational and patient factors [47].

1.3.3 Chronic heart failure as an exemplar

In this thesis, CHF is used as an exemplar condition in order to develop a suite of appropriate, relevant and accessible outcome measures to inform patients, providers and health care system. Beyond a diagnosis of CHF, the issues related to CHF are germane to many conditions of both malignant and non-malignant origin [48]. Many of the issues faced by people with CHF strongly relate to ageing, frailty and comorbid conditions and outcomes are influenced by socio-economic and cultural factors [26]. Conditions, such as chronic obstructive pulmonary disease, diabetes and many cancers have many similarities with CHF from the perspective that they are chronic progressive life limiting illnesses, cause a high symptom burden and have a significant impact on caregivers and the health care system [48]. There is a clearly defined need for investigating outcome assessment in chronic illnesses where often the patients' perception of QoL are adversely impacted despite the improvement in more traditional outcomes such as mortality. Moreover, the complexity of clinical care and the assessment of additive treatments increase the need for increasingly sophisticated forms of measurement. These data need to be relevant and interpretable to patients, providers and health care systems. For example, in the United States (US), the Patient-Centered Outcomes Research Institute (PCORI) has been established by the US Congress to conduct research to provide information about evidence to help patients and their health care providers make more informed decisions [49]. This is largely driven by

the perception of individuals and the assessment of patient reported outcome measures [2] which provide the view of the individual.

1.4 Outcomes

Outcomes are defined as the results of care [50]. They are used to gain understanding of CHF at every facet of its trajectory and any associated health care intervention. Outcomes are utilised at all levels of care by describing, interpreting and predicting effects of health care practices and interventions. Outcome assessment is directed at meeting three objectives; (1) to assess the efficacy of treatment/care of individuals as well as effectiveness; (2) to help in managing health service delivery and monitoring its quality; (3) and to support priority setting and policy development [50].

Traditionally clinical outcomes such as mortality and morbidity have been used in clinical trials and also widely reported as progress against the burden of CHF at all levels of care. Generally the reason for frequent use of mortality and morbidity may have been due to the fact that they reflect the natural history of the disease [51]. With the epidemiologic transition from infectious to chronic diseases and increase in life expectancy, these outcomes are seen to be increasingly inadequate [2]. Although they are intuitively easy to understand, these clinical outcomes have been associated with crucial shortcomings such as limited insight to the values of patients. Moreover, many individuals are living with more than one chronic illness. Consequently there is a growing recognition to supplement outcomes such as mortality and clinical events such as morbidity with PROs such as QoL and symptoms to facilitate understanding not just of survival but also of suffering caused by CHF.

1.4.1 Patient reported outcomes

PROs refer to information reported directly from the individual affected by a health condition and treatment received. It is an umbrella term to capture outcomes that are based on patients' direct perception, interpretation and evaluation of their condition as well as care and services received [52]. Hence PROs encourage patients' participation. PROs extend beyond traditional outcomes to include results

that are significant to patients. In fact, PROs such as patients' perceptions of their health have been found to be important indicators of health [53]. Usually, PROs are a multidimensional construct assessing various perspectives on disease and treatment including patient preferences, QoL, symptoms, functional status, psychological well-being, treatment adherence, and satisfaction with treatment by means of a self-completed questionnaire. Although there are clear differences in definitions, PRO measures, QoL or HRQoL questionnaires are commonly used interchangeably [54].

The aim of PROs are to assess the patient's perspective of health, illness, and the effects of health care interventions in a reliable, valid, acceptable, and feasible way [55].There is a growing belief that PROs have the potential to improve CHF care by promoting patient centred care [55]. By assessing PROs in a rigorous and valid manner, individual patient care will improve as better information about the effect of care is available [55]. Subsequently this will improve the decision making process [55]. Furthermore PROs have the potential to influence health policy and the allocation of healthcare resources [56]. However, in spite of the endorsement in policy, data suggests that they are not widely influencing practices [57]. In using PROs, many challenges exist such as concerns over the quality of the measures, and the wide variations in standards of study design and reporting that may lead to difficulties in interpreting PRO data [55].

1.4.2 Patient important outcomes

Patient important outcomes (PIO) can be defined as outcomes that patients notice, cares about and for which they would be willing to undergo a treatment with associated risk, cost, or inconvenience for it to be the only thing that change [58]. The drive to improve the quality of care has led to the realisation of the importance of patient's perspective and hence the use of PROs. However PROs are not the same as PIO. Despite the importance of PROs as an outcome measure in CHF, PROs currently available have been developed and driven predominantly by clinicians or researchers [59]. It is also important to remember that PROs may not be the only outcomes that they value. Patients, at the centre of care, should be able to identify

an outcome important to them that might not have been considered by practitioners or even researchers.

With a growing interest in patient centred care, seeking to measure outcomes that are important to patients is a natural consequence [49]. It has been suggested that clinical outcomes such as mortality and morbidity in addition PROs such as satisfaction with care and functioning and health status need to be tracked for patient centred care [7].

1.4.3 Outcomes from different perspectives

In assessing and monitoring health care effectiveness and efficacy, a range of outcomes important to key stakeholders of health care (patients, provider and the health care system) need to be considered especially if they are to influence policy, practice and future research. The perceived importance of different CHF outcomes will vary from the vantage point of patients, providers and system. From the perspective of patients, the QoL may be the most important outcome, whereas clinical outcomes may be the most frequently used amongst health care providers. For health care systems, outcome of the greatest consequence may be the economic cost. One of the main areas of interest would be whether the outcomes deemed to be important to patients are also important and meaningful to providers and health care system and the possible methods of integrating these outcomes.

It has been recognised no single outcome can capture all elements of a complex syndrome such as CHF [60] nor provide all required information for all stakeholders of CHF care. Assessing outcome measures that include PROs to develop a core set of outcome measures that are relevant and meaningful to all key stakeholders would potentially influence policy, practice and research. In addition, integrating these data into a single composite outcome may be a step forward in providing robust but simple information that reflect the benefits and burden from the viewpoint of each stakeholder group.

1.4.4 Composite outcome

A composite outcome is where multiple outcomes are combined into a single outcome measure [61]. Implicit in the definition is an expectation that each of the component outcomes would measure the same underlying pathophysiology, but be different enough that they add a dimension to the measurement of the disease process that has not been contributed by any other component outcome [62]. The composite outcome derived would consist of a set of outcome measures meaningful to all participants of the health care.

1.5 Study aims

Using CHF as an exemplar, this thesis reviews, integrates and synthesizes outcome measures to propose a core set of outcomes that takes into consideration patient, clinical and organizational perspectives. This thesis also extends the concept of PROs to considering the option of those that are important and meaningful to the patients (PIOs). Furthermore, current models that have tried to incorporate outcomes that may be more meaningful to a wider variety of stakeholders will be tested using data from a contemporary CHF clinical trial. This objective was achieved by conducting a series of sequential studies. Specifically this study sought to:

- Examine patient reported outcomes in clinical management and in clinical research (Chapters 2 and 3).
- Investigate patient important outcomes, their utility, relevance and acceptability amongst patients, clinicians, researchers and administrators (Chapter 4)
- Test composite outcomes model that integrate patient important outcomes using the data from clinical trials research (Chapter 5).

1.6 Overview of the thesis structure

To achieve the aims above, Chapter Two is an integrative review of PROs as an outcome measure to influence policy decision. The PROs measure, for example, health related quality of life (HRQoL), symptom, functionality and spirituality will be explored for conveying important and unique information for CHF policy decision.

Despite recognition of PROs and exponential usage in clinical trials, its use is limited in clinical practice and minimal in policy domain. This chapter describes how PRO measures compliment the traditional clinical outcome measures in conveying important information for policy makers to enact the vision of a patient centred care.

Despite multiple utility of PROs measure in CHF, the primary area of application has been in clinical trials, particularly of HRQoL. Chapter Three will be assessing the methodological and reporting quality of HRQoL assessment in CHF clinical trials. This chapter addresses methodological and reporting rigour of HRQoL assessment.

Chapter Four provides a review of the PIOs in CHF across the illness trajectory. This is to examine the meaningful outcome measures applied in CHF and identify the strengths and weaknesses of approaches to each outcome measure. Furthermore, this chapter recommends the core set of outcomes consisting of PIOs that are also meaningful to providers and health care system.

Chapter Five reports on methodological and weighting issues in composite outcomes combining set of PIO measures identified in Chapter Four using data from the Which Heart failure intervention is most Cost-effective & consumer friendly in reducing Hospital care (WHICH(?)), a multicenter, randomised controlled study [63].This chapter proceeds to describe derivation and its implication on interpreting these composite outcomes.

Chapter Six provides a discussion of the study findings and provides conclusions based on the investigations undertaken as part of the doctoral thesis. It will particularly focus on summarising and discussing the outcome assessments and its implication to policy, practice and research.

1.6.1 A note on the format of the thesis

References are presented at the end of each chapter and publications related to chapters are presented in the appendices with the permission of the publishers and ethical approvals. In order to facilitate reading and interpretation, some issues are repeated in specific chapters.

1.7 Conclusion

This chapter has described the inadequacy of traditional outcome measures to evaluate health outcomes in common, chronic illnesses with a high comorbidity burden. In addition, this chapter has depicted the burden of CHF and the need to capture the unique perspective of the patient in clinical and therapeutic interactions and also derive outcomes that are meaningful to patients, clinicians and policy makers especially in the management of chronic conditions. The following chapter will use the method of an integrative review to identify and describe the importance of PROs to inform policy decision.

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Chapter 2 The role of patient reported outcomes in informing health policy

2.1 Introduction

Chapter 1 provided an introduction to the thesis and emphasised the importance of PROs in driving efficient, effective and equitable services [1]. Traditionally, a range of outcome measures have been used to communicate health care quality including treatment effectiveness and patient centeredness using incidence, mortality and morbidity [2]. However, these measures fail to express the burden experienced by CHF patients. One of the reasons may be that they focus exclusively on the clinician's perspective of CHF treatment as these measures are derived from data sources documented by the clinicians and other health professionals. Accordingly, there is clearer information on CHF mortality or hospitalisation than on issues such as HRQoL or satisfaction with care as experienced and reported by patients [3].

To date, the focus on PROs has been from clinical trials and individual studies, yet there is limited inclusion of the patient perspective in routine clinical decision making. Outcome measures at the patient level facilitate policy makers to balance the societal benefits and costs [4]. Moreover, a number of qualitative studies and reviews have underscored the need to focus on individual's needs. The subjectivity of this assessment and the inability of health professionals to evaluate this for their patients have been demonstrated in many settings. The US multicentre SUPPORT (Study To Understand Prognoses and Preferences for Outcomes and Risks of Treatment) study [5] has provided evidence of the disparity between physicians' description of severity of symptoms and that of patients.

Consequently there is a need to track and analyse a range of outcome measures important for not only individual clinical decisions but for policy decision as well. In addition, an informed decision making at macro level will reduce unnecessary expenditure by minimising overuse/misuse of health care services or more critically, underuse that result in dire consequences for the individual. Although there is a gradual recognition of the relevance of PROs in decision making in the health care system, PROs are not routinely collected and analysed and hence PROs have had limited influence on policy decisions [4].

2.2 Global burden of chronic illness (Non-communicable diseases)

At a global level the burden of non-communicable diseases (NCDs) are increasingly recognised. NCDs are responsible for 63 percent of all deaths around the world [6]. Not only do NCDs exert an enormous health problem, but they also have serious socioeconomic consequences [7]. Therefore mechanisms of monitoring surveillance and outcome assessment are needed [8]. Increasingly governments and policy makers are presented with treatment allocation challenges. Technological innovation is occurring at an unprecedented rate in cardiovascular care challenging resource allocation and workforce availability. Increasing fiscal constraints and paradoxically the need to provide innovative, acceptable, state–of-the-art care is complex [8]. Balancing these needs in the context of a consumer and market driven society is a delicate balance for health care policy makers and health professionals, particularly within a context of the need to decrease health disparities and promote equity of access.

This chapter presents an integrative review to summarize how PROs have been defined, measured, and used in CHF research and discusses their implication in policy decisions. Moreover, it provides a discussion of the Innovative Care for Chronic Condition framework as a mechanism for improving outcomes at a macro, meso and micro level for chronic conditions [9].

2.3 Rationale for the increased focus beyond morbidity and mortality

Ageing and the increasing burden of NCDs, including heart disease, respiratory conditions and stroke are influencing strategic policy initiatives in both developed and developing countries [10]. These factors also challenge clinicians and policy makers to consider health and social outcomes beyond traditional concepts of morbidity and mortality. Rapidly growing disciplines, such as health economics, strive to balance parameters of demands, costs, and benefits relative to patient outcomes and treatment allocation [1, 11]. Yet there is discussion and debate of these approaches and the need to capture the needs at the level of the individual.

Clinicians and policy makers are increasingly aware of the complex interplay of social, economic, physiological and policy factors in determining health outcomes

[12-14]. The dilemmas confronting contemporary society underscore the need to increase the links between researchers and policy makers to develop, evaluate and implement appropriate interventions. [15] As well as assessing clinical outcomes, we also need to capture the unique perspective of the individual and their social determinants of health, to effectively inform health care planning. [16] This is of particular significance in chronic and aged care conditions where psychological and social issues play an important role in aetiology and prognosis [17, 18].

Balancing treatment burden in the elderly is of concern and often gains in longevity are not matched by symptom relief and QoL. [19] The health status of a population has traditionally been measured in terms of mortality and morbidity rates. Yet, with the epidemiologic transition from infectious to chronic diseases, quantifying health in terms of death and disease rates is seen to be increasingly inadequate. [20] Moreover, the ageing of the population means that a greater proportion of the population will receive treatment for chronic disease for a longer period of time. In chronic diseases, the goal of treatment commonly changes from cure to control of symptoms through targeted interventions [21].

2.4 Patient reported outcomes

As discussed in Chapter One, the increasing complexity of treatment allocation, acceptability and utility makes the views of consumers more critical in intervention development, evaluation and health service planning. [22] One way to achieve this perspective is through assessing PROs. This term refers to information and measures reported directly by the individuals affected by a health condition, treatment or life experience [23]. PRO captures the patient's perceptions of the broad spectrum of diseases and treatment outcomes. HRQoL is one of several types of PROs. Others may include symptoms, treatment adverse effect, functional status, and overall well-being. For example, capturing information to bathe without assistance and participate in activities of daily living is important in determining the impact of an intervention. Further, if an individual is unable to either fill their medication prescription or open the medication container pharmacotherapy is unlikely to be effective.

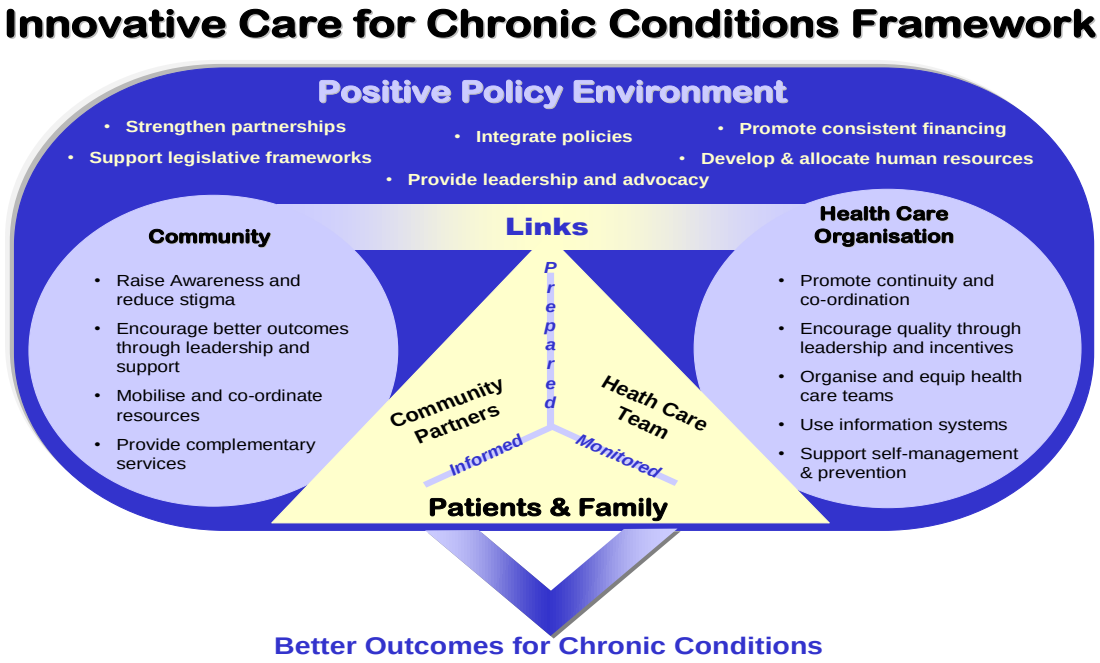
Despite benefits of a proposed treatment there is also the risk of an intervention having deleterious effects on the individual's QoL and capacity to undertake activities of daily living. In such a case, the cure can be worse than the disease. Likewise, extended life can mean living for a prolonged period with a disability [24]. As complexity, burden and cost of treatment escalates, it is vital that patients and their families, clinicians, policy makers and funding bodies have a realistic expectation of outcomes, not merely in relation to the physical, but from a psychological and social dimension as well [25]. Gathering the unique perspective of patients and their families is paramount. These data will be crucial in informing policy makers to plan and implement strategic initiatives. Therefore it is increasingly an important consideration that the unique perspective of the patient be represented not only individual clinical encounters, including patient assessment, but also in health policy, clinical trials and health service evaluation [26].

Patient reported outcomes can be either generic or specific to a clinical condition or disease state. Often the term "PROs" has been used to refer to the concept being measured, the instrument used to measure the concepts and the actual endpoint. There is a need to distinguish the concept and outcome one is attempting to measure and the endpoint for statistical analysis [27]. It is important to remember the PROs concept is the very specific goal of the measurement. It is vital to have sufficient evidence that PRO concept is adequately measured by a PRO instrument [28]. In recent decades there has been an exponential growth in the measures and it is important to consider not only the psychometric properties but also the utility in making treatment decisions and policy development.

2.5 Innovative Care for Chronic Conditions framework

The Innovative Care for Chronic Conditions (ICCC) framework (Figure 2.1) has been empirically derived to help reorient health care systems to manage the demands of the rising burden of chronic conditions around the world [9]. This model has been associated with improved health outcomes at the level of the patient and health care system [29]. At the centre of the framework is the healthcare triad (micro level of care); the partnership between patients and families, health care teams, and

community supporters. This recognises the importance of patient centred care and recognises the need for partnerships in improving health outcomes [29].



Building Blocks for Action Innovative Care for Chronic Conditions: Global Report. World Health Organisation 2002.

Figure 2.1 The Innovative Care for Chronic Conditions (ICCC) framework

The Chronic Care Model involves six pillars: community focus where health care services interface with the community; health systems that support management of chronic conditions; self-management support incorporating a comprehensive behavioural strategy which empowers and prepares people to manage their health and health care; delivery system redesign, where roles and expectations are clarified; decision support with ongoing development of strategies to manage decision making; and clinical information systems, allowing the tracking of patients. Integral to each of these dimensions is the assessment and evaluation of the perspectives of patients.

To achieve optimal outcomes this triad needs to be supported by the broader community and the integrated health care organisations (meso level of care). This in turn needs to influence the broader positive policy framework (macro level of care) and to be influenced by them. It is contingent on every member of triad

(patients and families, health care teams, and community supporters) being informed, and to maintain communication and collaboration.

The ICCC framework emphasizes the importance of patients and families, forming one-third of the key 'partnership triad' at the most basic level. Furthermore, because management of chronic conditions requires lifestyle and daily behaviour changes, emphasis needs to be placed on the patient's central role and responsibility in health care. When we refer to the patient, we consider family members and carers as part of this unit. Inclusion of this important dimension is contingent upon developing and testing of a model that measure the patient's unique perspective.

2.6 Value of patient reported outcomes in policy decision

As discussed above, PROs in the context of health care have become an increasingly important focus of regulatory bodies and health care administrators [25]. The potential for interventions and treatments to be assessed from the perspective of the patient through validated psychometric measures is a critical issue for clinical practice, outcome evaluation and research. At a conference to assess the contribution of the Agency for Health Care Policy and Research (AHCPR) in enhancing outcomes, it was concluded that researchers and policy makers need to build upon descriptive studies and methodological advancements with the goal of measurably improving outcomes, quality, and efficiency of care [30]. Developing this science is dependent upon collaboration between consumers, academics and clinicians from a range of disciplines, particularly health sciences and biostatistics, as well as policy makers and administrators.

2.7 Purpose of the review

To provide more in depth discussion of PROs and how these can inform the metric that assists policy makers in developing and implementing health policy within the context of CHF, an integrative review was undertaken. As mentioned in previous chapter, living with CHF commonly includes high levels of ill-health, disability and

mortality placing a heavy burden on health services. A number of qualitative studies and reviews have demonstrated that that living with CHF was characterized by distressing physical and emotional symptoms, compromised physical functioning, altered social and role dysfunction and living with uncertainty [31-35] . Given the nature of debilitating symptoms, and their potential impact on physical, social and psychological aspects of life, assessing PROs in CHF seems appropriate.

This review summarizes how PROs have been defined, measured, and used in CHF research and identify their possible implications for policy initiative. The electronic databases CINAHL, Medline, EMBASE and the Internet were searched using key words including 'heart failure', 'instruments', 'psychometric instruments' and 'patient reported outcomes.' Furthermore the reference lists of published materials were hand searched for additional data sources. The aim of the review was to explore patient reported outcomes measures in CHF that may provide new insight in policy decisions. A range of measures contributing to the impact of the outcomes of CHF, such as medication adherence and self-management were explored. Inclusion criteria were those papers that explored PROs measures that would provide new dimension in outcomes of CHF. Exclusion criteria were papers not published in English. Abstracts were appraised that most fitted the aims of the review and met the inclusion criteria.

2.8 Utility of patient reported outcomes

Examples of commonly used PROs were provided to illustrate the importance of including these issues in policy decisions. Table 2.1 provides examples of the constructs that assess the impact of CHF on an individual, ranging from limiting activities of daily living through to existential distress. Although this list is not exhaustive it provides insight into the range of measures available. Despite many potential uses of PRO measures in CHF, the primary area of application has been in randomised clinical trial investigation, particularly HRQoL. This is in line with the recognition that the changes in physiological measures may not always translate into a tangible benefits perceived by the patients. On closer inspection of these measures, outcomes important to patients are affected not only by symptoms and

disease severity but also by a complex interaction of physical, social and psychological factors. By incorporating patients' perspective they account for differences, subjective as well as objective among individual patients and to cater for patient's preference. When the individual is unable to complete such measures, the use of proxies can be considered.

Table 2.1 Examples of PROs in CHF

Construct	Definition	Disease specific examples	The impact of CHF on an individual
Health related quality of life (HRQoL)	HRQoL concerns attributes of life valued by patients, such as level of comfort; sense of well-being; ability to maintain reasonable physical, emotional, and intellectual function; and ability to participate in valued activities.[36]	Examples of disease specific instruments include the Minnesota Living with Heart Failure Questionnaire [37] the Chronic Heart Failure Questionnaire (CHQ) [38] and the quality of life questionnaire in severe heart failure (QLQ-SHF) [39] Kansas City Questionnaire [40]	Patients with CHF often experience a burden of disease that has a negative effect upon their health-related quality of life. The important goal of increasing the length of healthy life demonstrates a change from just measuring mortality and morbidity to also include health related quality of life [41]
Self-reported functional status	Self-reported functional capacity or status usually refers to ability to participate in everyday activities, in distinction to psychological aspects of quality of life such as perception of health. [42]	Self-reported functional status in CHF patients is usually assessed by using subscales of quality of life questionnaires. [39]	How much symptoms (and psychologic distress) commonly associated with CHF limit physical, social, role, and mental function. It also incorporates the effects of extraneous factors such as personal motivation which may not be able to be captured by clinical outcomes [43]
Psychological Distress	Psychologic distress refers to feelings of dysphoria,	A variety of self-report and interview measures have been used to assess levels	It is only recently that attention to the psychosocial issues of CHF including stress,

Construct	Definition	Disease specific examples	The impact of CHF on an individual
	anxiousness, worry, and other negative psychologic reactions to illness ([43])	of depression in CHF including a range of generic instruments. The CDS is a self-report, 26-item self-rating scale, which measures depression specifically in cardiac patients and may be used to measure depression in patients with CHF. [44] However, it should be noted that somatic depression symptoms of fatigue and insomnia included in the CDS are also primary symptoms of CHF.	anxiety and depression had increased. These factors have been related to coping styles and physical health of patients with CHF. Besides predicting cardiac events and affecting mortality, it is possible that depression may contribute to the high readmission rates for patients with CHF. [45, 46]
Spiritual/existential	Reference to spiritual and existential issues refers to the search for meaning, purpose and fulfilment in life. [47, 48]	Spirituality in HF patients is assessed by Spirituality Assessment Scale (SAS), which is a generic instrument or using a qualitative method which allows a deep understanding of the social and illness experience of HF patients. [49]	Spiritual beliefs serve as a buffer for stressful physical and emotional events associated with chronic illness in HF patients [50]. Spirituality has also been linked with the adjustment of patients with severe CHF. [48]
Self-care	Self-care involves a process of maintaining health through positive health practices, and managing illness and disease. [51]) Patients with a chronic illness such as CHF engage in self-care	Self-Management of Heart Failure instrument developed by Riegel et al for evaluating the self-management abilities of HF patients. [52]	Self-care can have positive lifestyle modification effect, on response to worsening symptoms and on coping with chronic illness. [53]. All of these will lead to fewer problems leading to readmission or unnecessary visits to

Construct	Definition	Disease specific examples	The impact of CHF on an individual
	primarily to manage what may be a precarious balance between relative health and symptomatic CHF.		emergency department. [53]
Self-efficacy	Self-efficacy is the judgment that individuals develop about their own ability to successfully perform a given behaviour.	The Heart Failure Self-Efficacy Scale–30 (HFSE-34) is a disease specific instrument and contains 5 subscales designed to measure self-efficacy with medications, diet, symptom control, and activity and HF readmissions. [54]	Self-efficacy has been demonstrated to be a marker of cardiac function and has been demonstrated to predict mortality and hospitalisation [55]. Self-efficacy is increasingly used as a predictor of behaviour and adherence. [56]
Satisfaction	Satisfaction can be defined as the extent to which individuals perceive either positively or negatively the impact or delivery of a health intervention. [57, 58]	There are no disease specific, prevalent, systematic, or statistically validated instruments for measuring patient satisfaction with CHF. Patient satisfaction has been measured only as a part of a battery of "outcome" measures, such as quality of life or health need assessment or satisfaction of particular interventions such as video-consultations. [59, 60]	Patient satisfactions can be used as an endpoint that explores affability, accessibility and availability of high quality care [61].
Treatment adherence	Adherence is defined as the extent to which a person's behavior	The HF Compliance Questionnaire (HFCQ) and its revised version (The	Poor treatment compliance among HF patients has been linked to increased mortality

Construct	Definition	Disease specific examples	The impact of CHF on an individual
	coincides with medical advice. It is a multifactorial process involving characteristics of the health care system, the individual, the treatment regimen characteristics, and the quality of the patient-provider interaction. [62, 63]	HFCQR) have been used to measure patients' adherence to medical regimen. [64]	and morbidity rates and increased health care costs associated with increased outpatients care as well as hospital readmission. [63]
Cognitive status	Cognition refers to those mental activities associated with thinking, learning, and memory. There is strong evidence to suggest multiple contributors to cognitive dysfunction in CHF. [65]	Increasingly validated measures of cognitive function, particularly those assessing executive functioning are used in CHF.[66]	It is estimated 25% to 50% of HF patients have cognitive impairment [65]. HF has been proposed a s a possible cause of cognitive function, expressed as a term 'cardiogenic dementia' [67]
Social support	Social support refers to the perception of both instrumental support and assistance psychologically and emotionally. [68, 69]	Social support has been assessed in CHF and identified as a predictor of outcome. [69]	Social support influences symptoms and functional status, health [perceptions [70]. It would facilitate management of symptoms such as fatigue and cognitive impairment. [36]
Carer outcomes	Carers play a critical role in supporting individuals with CHF and this can have both positive and negative health, social and	A number of caregiver instruments are available to assess caregiver outcomes. [72]	Caregivers play an important role in the care of patients with HF, hence caregiver contributes to patient outcomes [73]. Lack of caregiver support has been shown to be

Construct	Definition	Disease specific examples	The impact of CHF on an individual
	psychological outcomes. [71]		associated with higher rates of hospitalisations for patients with CHF [73]
Social capital	Social capital relates to networks and relationships in society based upon normative values that enable collaborative and cooperative activities for mutually beneficial outcomes. [74]	The issue of how social capital is lined to health and disease including CHF remains uncertain although the strong association between social determinants of health and outcomes make this of an increasing interest and concern.[75]	Social capital is associated with quality of life especially in an old age [76]. Also social capital has been shown to be linked to health care utilisation and demand [77]
Resilience	Resiliency refers to a person successfully adapting to adverse life events or circumstances or both. [78]	Resilience of the patient to CHF is poorly studied, although hope has been described. [79]	Resilience would minimise demoralisation, depression and vulnerability in CHF patients [80]
Needs	Needs assessment is a tool for evaluating perceptions of health status, determining patient satisfaction and treatment plans. [81]	Nottingham Health Needs Assessment (NHNA) has been designed to specifically assess the health needs of cardiac patients. [82] The Heart Failure Needs Assessment Questionnaire has also been developed specifically for individuals with CHF. [81]	Provides information on patients' perceptions of their existing health status and unmet needs in current management plan [81]. Guides planning and projection of needs of patients and population [81]

Importantly, PROs extend beyond traditional clinical efficacy and adverse effects and represent the patient's perspective on the impact of disease and its treatment

on daily functioning and wellbeing. [83] In many situations patient report is the sole source of data on frequency and severity of symptoms and also the side effects and the impact of treatment on functioning and well-being [84]. Hence they are managed and monitored almost entirely on patient reports. Indeed in conditions where there are no physical or physiological markers of disease activity, PROs become the outcome of choice for evaluating disease activity and in providing comprehensive understanding of severity of symptoms and their impact on daily functioning and well-being. Palliative and supportive care is a striking example of such a strategy [80, 85-87].

However, it is not uncommon for there to be a mismatch between the patient's perception and the clinician's assessment [81]. For example, in some instances the patient's perception of CHF and disease severity has also been overestimated when compared to the physician's clinical findings [88]. This incongruence may be due to the validity of tools used to assess patient perception or, an underestimation by clinicians of patient's with CHF.

Therefore valid and reliable PROs can be an important communication tool. These measures provide a useful way to gather and communicate evidence about treatment risks and benefits. This information can be used to highlight particular treatment benefits or to provide a way to differentiate the patient benefits among competing treatments with similar clinical efficacy [89]. This will assist clinicians in providing patients with better information about potential effects of treatment, and thus lead to better treatment decisions. Data derived from PROs can also enable patients to increase their understanding about their illness and treatment risks and benefits. This is also a potentially useful strategy in increasing individuals' participation in their own treatment and in health care decision making. Patient adherence is a major impediment to the effectiveness of therapies. Increased patient satisfaction with a treatment has been shown to be related to adherence [17]. Accordingly, evaluating satisfaction with treatment may assist health care providers in understanding the issues influencing treatment adherence and may

help identify aspects of the management plan that require improvement to enhance long term treatment outcome [90].

The ICCC framework (Figure 2.1) describes the importance of community and policy aspects of improving health care for chronic conditions [91]. This model highlights the importance of considering discrete yet linked attributes at the micro (patient and family), meso (health care organisation and community), and macro (policy) levels, underscoring the need for a multifaceted approach to health care outcome assessment. To date, a comprehensive model for health service evaluation including all these critical elements has not been tested.

Patient assessments are important elements of the evaluation of treatment impact, alongside other clinical indicators. Bioethics has emphasised the importance of the patient's point of view in health care decisions through its call to respect patient autonomy. Outcome research has specified the importance of the patient's perspective on the goal of medical care in its bid to accentuate patient-centred outcome such as QoL [81]. It is recognised that linking patient-reported health with physiological markers of disease provide not just unique information in patient care, but also help to determine the severity of disease and monitor the trajectory of illness [92]. These factors are also important in informing cogent policy decisions.

It is hard to dispute that the science of PROs is advanced, as illustrated in the vast numbers of psychometric instruments available to assess these items. Perhaps what remains is the greatest challenge; moving assessment of these constructs beyond the research setting to routine clinical practice and perhaps as a part of administrative data collection that will inform clinical and policy makers.

The relevance of the applicability of clinical trial evidence to real world populations is commonly questioned [93]. Often participants in clinical trials are commonly younger, have less comorbid conditions and commonly do not have the challenges of poor health literacy and cognitive impairment that impact on outcomes of CHF [94]. This conundrum is illustrated in the adverse events related to

pharmacotherapy when agents move from the clinical trial to the usual care setting [95].

Registry data provides a useful insight into real world situations that can provide policy makers with reliable and valid data to inform policy decisions. A number of registries have provided useful data to inform CHF management in the real world setting [96-100]. Many of these registries provide useful data – particularly relating to how factors such as socioeconomic determinants, level of insurance, and ethnicity impact on health related outcomes. [101] Data for these registries is often collected from administrative data sets that do not routinely use PROs. Including valid and reliable PROs in these data sets may be useful in health service planning.

2.9 Innovative Care for Chronic Condition framework and policy decision

As shown in the ICCC Framework in Figure 2.1, a Positive Policy Framework is contingent upon understanding the needs of patients and their families. This can be achieved through a range of means, such as community consultations, representations of democratically-elected candidates and lobbying from particular consumer organisations. A potentially more equitable, just, reliable and valid mechanism would be to include PROs in routine clinical assessments, clinical trials and registries to allow an informed decision on how conditions, treatment and health care interventions impact on the lives of individuals and their families. For example, in Australia, the most rapidly increasing population are centenarians - many of whom will endure and die of CHF. Yet, we know little of their needs and service planning requirements. [102] Further, the development of reliable and valid metrics that allow for the integration of micro, meso and macro elements of health service delivery are needed. Health care policy, often constrained by partisan politics and influence of powerful lobby groups, can struggle to keep pace with the strategies needed to administer and monitor the increasing expense and complexity of healthcare [103]. In CHF, the development of innovative treatments, such as implantable cardiac defibrillators, left-ventricular assist devices have outpaced the debate and discussion of the applicability and relevance to particular groups [80, 104]. Despite benefits some patients may derive from these medical

interventions, the default plan of providing these devices or procedures regardless of patient's wishes and priorities need to be re-examined by policy makers. Furthermore, their use entails substantial financial, physiological, and psychological costs to patients, health care system and community in general.

Policymakers and clinicians alike need to allocate limited resources to patients with CHF to serve their interests and perspectives. Understanding the impact of these interventions on individuals is likely to be critical in the future and require extensive debate and discussion. Evidence based policy making is dependent on the weighting of a range of issues including cost, measures of effectiveness, equity and also the perspectives of patients and caregivers. Moreover, it is important to consider the use of PROs in individuals who are cognitively impaired or from culturally and linguistically diverse groups [36, 105, 106].

2.10 Chapter summary

This chapter has summarised PRO measures and their utility in CHF research and considered the implications for policy initiative. It has demonstrated that there a numerous PROs assessing a diverse range of constructs. Effective policy and planning of health care services is dependent on being informed of the impact on the individual and their families. This should be derived from prospective, rigorous measures not ad hoc views and more importantly the sole perspective of health professionals.

The ICCC has been introduced as an important framework to improve the management of chronic illnesses. This model is designed to compel policy makers to make decisions about service supply and health care spending that reflects the balance of extending life with improved quality, a critical issue considering the increasing global burden of chronic illnesses. As HRQoL is considered to provide a multifaceted perspective of the individual living with a condition, the following chapter will review the methodological and reporting rigor of HRQoL. .

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Chapter 3 Methodological and reporting rigour of health related quality of life

3.1 Introduction

The previous chapter has identified and discussed wide range of PROs that would be useful in incorporating a person centred approach to care. As the burden of chronic conditions increase as the population ages, a need to develop and refine the metrics that includes the perspectives of patients at an individual and a population level becomes critical. Effective evaluation of the efficacy of health care intervention, treatment and planning will lead to health policy decisions on service provision and health care spending that will foster extending life with improved quality.

As discussed in Chapter Two, there are numerous PRO measures in CHF with the aim of increasing the patient's voice in their own health care. The use of such instruments, especially those measuring HRQoL has increasingly been acknowledged as crucial for evaluating the overall treatment effectiveness in clinical trials. Information such as physical and psychological problems, adverse effects of treatment, and social limitations are invaluable as they provide patient's perspective [1].

PROs as used in clinical trials have highlighted a wide range of benefits if applied in clinical practice, such as increase health practitioner's awareness of and ability to address patients' concerns and their preferences [2] and improve communication [3] and hence support shared decision making [3]. Despite these critical benefits, the translation of PROs from clinical trials to their use in clinical management has been limited. The reason for this slow uptake may be due to the heterogeneity in reporting of key HRQoL methodological factors in clinical trials which may have led to inability to appreciate or to interpret these measures competently amongst health care providers [4, 5]. Moreover, there is potentially inherent scepticism of health professionals and policy makers on the utility of this approach. Investigating the intent and psychometric approaches is necessary.

There are currently several generic and disease-specific HRQoL questionnaires used in CHF trials. Examples of generic measures used in CHF trials include The Medical

Outcomes Study (MOS) Short Form 36-item Health Survey [6, 7]and Sickness Impact Profile[8] and European Quality of Life instrument (EQ 5D) [9]. Measures of heart failure specific measures include Minnesota Living with Heart Failure Questionnaire (MLWHF) [9] and the Kansas City Cardiomyopathy Questionnaire [10] to name a few. They have all demonstrated acceptable levels of reliability, validity, responsiveness and acceptability for CHF population [11]. However reporting HRQoL in clinical trials requires more than specific information on the psychometric robustness of the tool for the specific trial population. Considerations such as on data collection, appropriate timing of assessment, adequate statistical analysis and outcome interpretation are all crucial to influence decision making.

3.2 Background

Chronic heart failure is a common, costly and resource intensive syndrome with a poor prognosis. Patients with CHF experience poor outcomes including severely impaired HRQoL [12]. Some studies have shown that patients with CHF experienced a poorer QoL compared to individuals with other chronic conditions [13, 14]. Many patients with advanced CHF also ascribe greater importance to the quality rather than the length of their life [15].

The number of clinical trials incorporating HRQoL assessment as an endpoint has increased in recent decades [16]. Increasingly CHF clinical trials focus on the benefit of "add-on" therapy for which the cumulative benefits may be an incremental gain in HRQoL, in spite of a limited impact on survival [17]. This increased focus on incremental benefit means that methods of assessment and reporting of endpoints such as HRQoL need to be rigorous and robust.

Although the purpose of measuring HRQoL in randomized control trials (RCTs) may have been to guide future patient care and treatment decisions, there is evidence of the limited influence of this approach on individual clinical decision making and/or treatment policies [18]. This may be attributed to inadequate reporting, low compliance with completing study measures, underpowered studies and variable quality in studies assessing HRQoL [19-21]. Furthermore, most clinical trials using HRQoL as an endpoint solely report psychometric properties and do not extend to

the issue of relevance of the measure nor to the rigor in measuring and reporting [22]. In spite of mushrooming of HRQoL assessment and as a consequence numerous reviews and meta-analyses on HRQoL in patients with CHF [16, 23-25] the methodological and reporting rigor of the HRQoL assessment in RCTs has not been described.

3.3 Problem statement

The purpose of this review was to assess the methodological and reporting of HRQoL in RCTs of pharmacotherapy in CHF, either as a primary or secondary endpoint using the "Minimum Standard Checklist (MSC) for Evaluating HRQoL Outcomes" [20] (Table 3.1). RCTs of pharmacotherapy were chosen for a number of reasons; for its potential for incremental therapeutic benefit [26]; of additive therapies [27]; and the fact that regulatory bodies such as the Food and Drug Administration (FDA) in the United States (US) request HRQoL data when making drug approval decisions [28]. Including non-pharmacotherapy and devices trials in this review would require additional methodological and reporting issues to be considered [29, 30]. This review also sought to investigate whether the methodological and reporting quality of HRQoL outcomes in RCTs has improved over time and as how HRQoL outcome is used in the study (primary vs. secondary outcomes).

Table 3.1 Level of reporting according to the Minimum Standard Checklist for evaluating Health related quality of life outcomes in pharmacological trials in CHF

HRQoL issue	Description
Conceptual	
A priori hypothesis stated	Assessed whether authors had a predefined HRQOL end point and/or stated expected changes because of the specific treatment.
Rationale for instrument reported	Assessed whether authors gave a rationale for using a specific HRQOL measure.
Measurement	
Psychometric properties reported[b]	Assessed whether a previously validated measure was used or psychometric properties were reported or referenced in the article.
Cultural validity verified	Assessed whether the measure was validated for the specific study population.
Adequacy of domains covered	Assessed whether the measure covered, at least, the main HRQOL dimensions relevant for a generic HF population and/or according to the specific research

HRQoL issue	Description
	question.
Methodology	
Instrument administration reported	Assessed whether authors specified who and/or in which clinical setting the HRQOL instrument was administered.
Baseline compliance reported[b]	Assessed whether authors reported the number of patients providing an HRQOL assessment before the start of treatment.
Timing of assessment documented	Assessed whether authors specified the HRQOL timing of assessment during the trial.
Missing data documented[b]	Assessed whether authors gave some details on HRQOL missing data during the trial.
Interpretation	
Clinical significance addressed	This refers to the discussion of HRQOL data being clinically significant from a

HRQoL issue	Description
	patient's perspective and not simply statistically significant.
Presentation of results in general	Assessed whether authors discussed the HRQOL outcomes, giving any comments regardless of the results (either expected or not).

Adapted from Efficace et.al.[20]

[a]When multiple instruments were used in a single study only one instrument had to satisfy the item in a checklist to have deemed to have met the health related quality of life issue for that study.

[b]High priority concerns that need to be satisfied

3.4 Methods

A search of the electronic data bases Medline and EMBASE was undertaken with the assistance of a health librarian. The search strategy used relevant keywords and Medical Subject Heading (MeSH) terms including 'heart failure' combined with 'health related quality of life', 'pharmacological therapy' and 'randomized controlled trials' restricted to articles in English (See *Appendix*). The search was restricted to 1990–2009 as it is in the last 20 years HRQoL has become a research area of interest. RCTs were considered to be eligible if HRQoL was explicitly designated as either primary or secondary endpoint. No restriction was set on type or number of HRQoL assessments in the study. Case reports, editorials, letters, commentaries, reviews, overviews and conference presentations were excluded along with cases where HRQoL assessment was included as a part of a composite endpoint. Studies with insufficient information regarding HRQoL assessment were also excluded. Potentially relevant articles were initially retrieved and if it was deemed appropriate the full text article were sought. Additional relevant studies were identified through a manual search of reference lists from previous review articles [16, 25].

The following information was extracted from included studies: Authors, main objective and study interventions, diagnosis, duration of the study, sample size, HRQoL used as primary/secondary outcome, description and type of the HRQoLs used and whether a power calculation was undertaken. When the primary outcome was not explicitly stated by the authors, it was defined as the one that was given prominence in the report or the outcome used for the sample size calculation.

3.4.1 Minimum Standard Criteria

Each RCT was evaluated according to the MSC [20] (Table 3.1). This checklist facilitates a critical review and interpretation of HRQoL outcomes by addressing the basic and essential issues that a given trial should possess to have sound and reliable HRQoL outcomes in clinical trials [20]. This checklist consists of 11 items grouped into categories addressing basic and essential methodological and reporting issues related to HRQoL assessment in clinical trials: conceptual,

measurement, methodology, and interpretation. The items were originally selected from the literature by consensus of HRQoL researchers and further refined by an additional independent panel of 30 experts in the field of HRQoL including clinicians, psychologists and statisticians [20]. Summative scores of eight and over, including three mandatory items (baseline compliance, reporting psychometric properties or referencing validation article and missing data documentation) on this checklist were considered as 'probably robust'. Scores between five and seven or not including all three mandatory items were classified as 'limited' and all other studies were classified as 'very limited'. If more than one HRQoL instrument was used, the study was credited for fulfilling a particular criterion/checklist if it was satisfied by any one of the instruments employed.

3.4.2 Statistical Analysis

To examine the effect of time on the MSC total score for HRQoL outcome, a linear regression model was used with the MSC total score as the dependent variable and the time of publication as the continuous independent variable. Prior to linear regression modelling, correlation analysis was used between MSC total scores, the year of publication, the usage of HRQoL outcome (primary vs. secondary), sample size and the duration of the study in weeks to identify any confounding variables. In addition, the publication year was classified as before and after 2005 to further examine any changes between these two time periods.

3.5 Results

A total of 392 studies were retrieved. After excluding 256 articles (Figure 3.1) not meeting the inclusion criteria 136 studies were included in the review. Of the 136 studies (See *Appendix*), 73 (53.7%) studies were published from 2000 to 2009. Most studies (n=112; 82.4%) used the New York Heart Association (NYHA) class to identify the patient group studied, with the most common grouping being NYHA II-III (46/112; 41.1%) followed by NYHA II-IV (30/112; 26.8%). The reported duration of the study ranged from 1 week to 235 weeks with 54 (40.0%) studies reporting 12 weeks or less. In some studies, this may include a run-in period (Table 3.2).

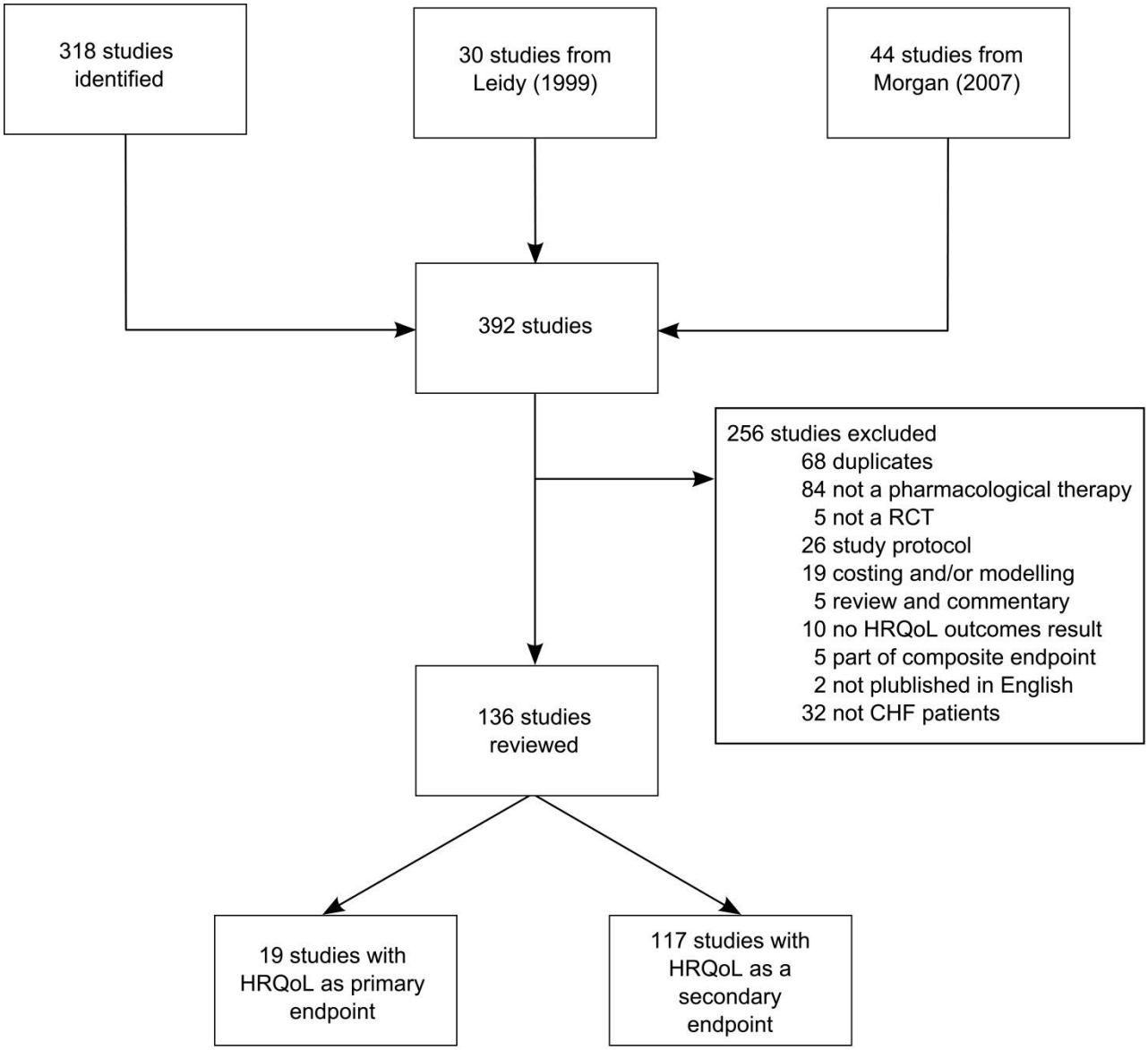

Figure 3.1 Flow diagram of study selection

Table 3.2 Characteristics of the studies included in the review. (n=136)

Characteristics	***n* (%)**
Sample size	
≤50	49 (36.0)
51 – 100	20 (14.7)
101 – 150	14 (10.3)
151 – 200	7 (5.1)
201 - 250	9 (6.6)
≥251	37 (27.2)[b]
Study Duration (in weeks)[a]	
≤12 wks	54 (40.0)
13 - 24 wks	24 (17.8)
25 - 36 wks	18 (13.3)
37 - 48 wks	5 (3.7)
≥49 wks	34 (25.2)
No. of questionnaire used per study	
1	103 (75.7)
2	14 (10.3)
≥3	19 (14.0)

[a]One study did not specify time frame.

[b]Percentages do not add to 100% due to rounding error.

HRQoL assessment was described as either a primary or co-primary endpoint in 19 (14.0%) studies (Table 3.3). However in only 4 of these 19 studies (4/19; 21.1%) the sample size was calculated based on a HRQoL hypothesis or the adequacy of calculated sample size to detect clinically significant HRQoL changes was considered. In more than half of these studies (10/19; 52.6%) a sample size calculation was not reported at all and in five studies (5/19; 26.3%) the sample size calculation was based on the other endpoints. Six of these studies (6/19; 31.6%) were sub-studies of larger RCTs [31-35]. For studies where HRQoL assessment was a secondary endpoint, only four studies (4/117; 3.4%) considered the adequacy of a calculated sample size on HRQoL assessment [36-38] while 64 studies (64/117; 54.7%) did not report on the sample size calculation at all. Of all 136 studies reviewed, 69 (50.7%) studies had a sample size less than 100 patients with the median sample size of 81.5.

Table 3.3 Characteristics of studies with health related quality of life as a primary/co-primary endpoint. (n= 19)

Authors	Year	Main Objective	Patient Group Description	Sample Size[a]	Intervention	Study Duration[b]	HRQoL Instrument	Power Calculation.	MSC class
1. Baligadoo et al.[39]	1990	To assess the effect of an inotropic agent on quality of life	NYHA III	10	Oral enoximone 150mg tds or Pl.	3 weeks	Disease specific HRQoL[c]	None	Limited
2. Rector et al.[40]	1993	To determine if the patients' perceptions of the effects of enalapril on their daily activities and sense of well-being were different from those of a group treated with hydralazine and isosorbide dinitrate.	NYHA I-III	804	Enalapril or Hydralazine and isosorbide dinitrate	216 weeks	MLWHF	None	Probably robust
3. Ekeberg et al.[32]	1994	To test the hypothesis that treatment with the ACE inhibitor enalapril is	4-6 months	132	Enalapril	26 weeks	Nottingham Health Profile	None	Limited

Authors	Year	Main Objective	Patient Group Description	Sample Size[a]	Intervention	Study Duration[b]	HRQoL Instrument	Power Calculation.	MSC class
		associated with a quality of life similar to that on placebo	after myocardial infarction				Physical Symptoms Distress Index Work Performance Scale Life Satisfaction Index		
4. Rogers et al.[34]	1994	To assess the quality of life of patients with left ventricular dysfunction for up to 2 years after randomization to enalapril or placebo	EF<=0.35	5025	Enalapril <=10mg or Pl.	104 weeks	Scales excerpted from validated instruments (POM), Functional Status	None	Probably robust

Authors	Year	Main Objective	Patient Group Description	Sample Size[a]	Intervention	Study Duration[b]	HRQoL Instrument	Power Calculation.	MSC class
							Questionnaire, SF-36)		
5. Cohn et al.[41]	1997	To describe the response of quality of life to vasodilating beta-blocker carvedilol in the subset of patients with the most severe impairment of exercise capacity	NYHA III-IV	131	Vasodilating beta-blocker carvedilol or Pl.	26 weeks	MLWHF	On HRQoL	Probably robust
6.Dorszewski et al.[42]	1997	To assess the effects of urapidil combined therapy on QoL, exercise tolerance and haemodynamic parameters	NYHA III-IV	36	Urapidil or Pl.	12 weeks	Modified MLWHF	On other endpoint	Limited
7. Bulpitt et al.[43]	1998	To measure quality of life (QOL) in patients with mild to moderate heart failure	NYHA II-IV	367	Angiotensin converting enzyme (ACE)	24 weeks	SIP	On other endpoint	Probably robust

Authors	Year	Main Objective	Patient Group Description	Sample Size[a]	Intervention	Study Duration[b]	HRQoL Instrument	Power Calculation.	MSC class
		treated with angiotensin converting enzyme (ACE) inhibitors cilazapril or captopril.			inhibitors cilazapril or captopril		POM Mahler Index of dyspnea-fatigue (Provider supplied) Health status index		
8. Newby et al.[44]	1998	To assess the effect of candoxatril, on exercise capacity, clinical status and quality of life in patients with mild to moderate chronic heart failure receiving angiotensin converting	NYHA I-III	110	Candoxatril or Pl.	12 weeks	Questionnaire assessing breathlessness, fatigue and well-being[c]	None	Limited

Authors	Year	Main Objective	Patient Group Description	Sample Size[a]	Intervention	Study Duration[b]	HRQoL Instrument	Power Calculation.	MSC class
		enzyme inhibition.							
9. Sanderson et al.[45]	1999	To compare the long-term clinical efficacy of treatment with metoprolol versus carvedilol	NYHA II-IV	51	Metoprolol or Carvedilol	12 weeks	MLWHF	On HRQoL	Limited
10. Cowley et al.[31]	2000	To measure health-related quality-of-life (HRQoL) in elderly symptomatic heart failure patients following treatment with an angiotensin II receptor antagonist (losartan) vs. an angiotensin-converting-enzyme (ACE) inhibitor (captopril)	NYHA II-IV	203	Losartan or Captopril	48 weeks	MLWHF SIP	On other endpoint	Probably robust

Authors	Year	Main Objective	Patient Group Description	Sample Size[a]	Intervention	Study Duration[b]	HRQoL Instrument	Power Calculation.	MSC class
11. Fung et al.[46]	2002	To compare the effectiveness of beta blockade in patients with heart failure and AF using MLWHF as a symptom measure	NYHA II-IV	63	Metoprolol 50 mg twice daily or carvedilol 25 mg twice daily in addition to standard therapy	12 weeks	MLWHF	On other endpoint	Limited
12. Lader et al.[35]	2003	To evaluate the effect of digoxin therapy on HRQoL	NYHA I-IV	589	Digoxin therapy	52 weeks	SF-36 Ladder of Life CES-D State Anxiety Inventory State Anger Inventory	None	Probably robust

Authors	Year	Main Objective	Patient Group Description	Sample Size[a]	Intervention	Study Duration[b]	HRQoL Instrument	Power Calculation.	MSC class
							MLWHF		
13. Lopez-Candales et al.[47]	2004	To investigate the need for hospice and palliative care programs among patients in end-stage heart failure who receive intermittent infusion of inotropes with MLWHF as a primary endpoint.	NYHA III-IV	73	Inotrope or Pl.	unknown	MLWHF	None	Limited
14. Majani et al.[33]	2005	To examine the effect on quality of life (QOL) of valsartan administered in addition to prescribed background heart failure therapy	NYHA II - IV	3010	Valsartan (160 mg twice daily) or placebo in addition to prescribed background therapy (beta-	156 weeks	MLWHF	None	Probably robust

Authors	Year	Main Objective	Patient Group Description	Sample Size[a]	Intervention	Study Duration[b]	HRQoL Instrument	Power Calculation.	MSC class
					blockers or angiotensin-converting enzyme inhibitors)				
15.Rajendran et al.[48]	2005	To compare the conventional with individualised digoxin dosing on quality of life and other various clinical outcome		41		52 weeks	MLWHF	None	Limited
16.Parissis et al.[49]	2007	To investigate the impact of levosimendan on QoL, physical activity and emotional stress in patients with severe CHF	NYHA III-IV	63	24h levosimendan infusion or Placebo		KCCQ DASI BDI	None	Limited

Authors	Year	Main Objective	Patient Group Description	Sample Size[a]	Intervention	Study Duration[b]	HRQoL Instrument	Power Calculation.	MSC class
							SDS		
17. Kourea et al.[50]	2008	To investigate the effects of recombinant human erythropoietin analog darbepoetin-a on quality of life and emotional stress	NYHA II-III	41	Darbepoietin-a plus iron or Placebo plus iron	12 weeks	KCCQ DASI BDI SDS	Post power calculation on KCCQ	Limited
18. Yip et al.[51]	2008	To assess the effects of delapril compared with captopril on quality of life, symptoms and LV global and regional function	LVEF> 45%	150	1) diuretics alone, (2) diuretics plus irbesartan, or (3) diuretics plus ramipril	52 weeks	MLWHF	On other endpoint	Limited
19.Fontanive et al.[52]	2009	To evaluate the effects of orally administered L-arginine	NYHA II-III	68	L-arginine or Placebo	12 weeks	MLWHF	On HRQoL	Probably robust

Authors	Year	Main Objective	Patient Group Description	Sample Size[a]	Intervention	Study Duration[b]	HRQoL Instrument	Power Calculation.	MSC class
		in CHF patients on quality of life, six minute walking tests and complete Doppler and echocardiographic evaluation.							

[a] As reported in the paper (this may be the number of patients recruited, the number of patients who completed the study, or the number of patients who have completed health related quality of life assessments).

[b] As reported in the paper (this may include a run-in period)

[c] Author developed

Although most of studies in this review used a single measure of HRQoL (n= 103; 75.7%), the number of instruments used in a single study ranged from one to five. In cases where multiple measures were used, the most common combination consisted of a condition specific measure and generic measure (9/21, 42.9%). The most commonly used HRQoL measure in CHF trials has been the Minnesota Living With Heart Failure Questionnaire (MLWHF) (n=83 studies) followed by a generic measure, Global assessment (n=31 studies where 26 studies were patient provided and 5 studies were provider assessed). In five studies where global assessment was provided by the physician three of these studies also included patient provided HRQoL. The only utility focused measure used in studies in this review was the EQ-5D (n=6). The results from discrete domains of an instrument were reported in 26 studies (19.1%). Similarly in 33 (24.2%) studies where multiple instruments have been used, results from individual instrument were reported. However, no study reported statistical adjustments for multiple comparisons.

3.5.1 Minimum Standard Checklist

Overall, 83 (61.0%) studies reported an a priori hypothesis or had a predefined HRQoL endpoint (**Error! Reference source not found.**). The rationale for instrument selection was reported in 34 (25.0%) studies. Eighty-six (63.2%) studies provided psychometric properties of the instrument used or cited the validation study. Interestingly, although 12 (8.8%) studies stated that the HRQoL instrument was developed for the purpose of their study, none of these studies reported the psychometric properties of the instrument or cited the source of a validation process. In 38 (27.9%) studies it was unclear whether the instrument was developed for the study or the authors were using an already established instrument.

While only 55 (40.4%) studies specified who and/or in which clinical setting the HRQoL instrument was administered, most of the studies (n=130; 95.6%) documented the timing of HRQoL assessment. Although 107 (78.7%) studies discussed the general result of HRQoL outcome in their discussion, only 57 (41.9%) studies addressed the clinical significance of the HRQoL outcomes. Only 23 (16.9%)

studies satisfied all three mandatory items of MSC. According to the MSC, 26 (19.1%) studies were considered ‘very limited’ in methodological and reporting of HRQoL results and 91 (66.9%) studies were evaluated as ‘limited’. Only 19 (14.0%) studies were considered to be ‘probably robust’. Table 3.4 Level of reporting a according to the (adapted) b MSC for evaluating HRQoL outcomes in CHF pharmacological trials by the duration of study period and by use of HRQoL endpoint

Table 3.4 Level of reporting according to the (adapted) MSC for evaluating HRQoL outcomes in CHF pharmacological trials by the duration of study period and by use of of HRQoL endpoint

	Publication year n (%)		HRQoL endpoint n (%)		Total
MSC Standard Checklist	**1990 - 2004 (n=89)**	**2005 - 2009 (n=47)**	**Primary (n=19)**	**Secondary (n=117)**	**(n=136)**
Conceptual					
A priori hypothesis stated	52 (58.4)	31 (66.0)	18 (94.7)	65 (55.6)	83 (61.0)
Rationale for instrument reported	17 (19.1)	17 (36.2)	7 (36.8)	27 (23.1)	34 (25.0)
Measurement					
Psychometric properties reported	56 (62.9)	30 (63.8)	15 (78.9)	71 (60.7)	86 (63.2)
Adequacy of domains covered	70 (78.7)	42 (89.4)	18 (94.7)	88 (75.2)	112 (82.4)

MSC Standard Checklist	Publication year n (%)		HRQoL endpoint n (%)		Total
	1990 - 2004 (n=89)	2005 - 2009 (n=47)	Primary (n=19)	Secondary (n=117)	(n=136)
Methodology					
Instrument administration reported	38 (42.7)	17 (36.2)	13 (68.4)	42 (35.9)	55 (40.4)
Baseline compliance reported	41 (46.1)	19 (40.4)	12 (63.2)	48 (41.0)	60 (44.1)
Timing of assessment documented	86 (96.6)	44 (93.6)	18 (94.7)	112 (95.7)	130 (95.6)
Missing data documented	44 (49.4)	17 (36.2)	12 (63.2)	49 (41.9)	61 (44.9)
Interpretation					
Clinical significance addressed	37 (41.6)	20 (42.6)	17 (89.5)	40 (34.2)	57 (41.9)
Presentation of results in general	71 (79.8)	36 (76.6)	19 (100.0)	88 (75.2)	107 (78.7)

	Publication year n (%)		HRQoL endpoint n (%)		Total
MSC Standard Checklist	**1990 - 2004 (n=89)**	**2005 - 2009 (n=47)**	**Primary (n=19)**	**Secondary (n=117)**	**(n=136)**
Checklist score					
Very limited	17 (19.1)	9 (19.1)	0 (0.0)	26 (22.2)	26 (19.1)
Limited	60 (67.4)	31 (66.0)	11 (57.9)	80 (68.4)	91 (66.9)
Probably robust[c]	12 (13.5)	7 (14.9)	8 (42.1)	11 (9.4)	19 (14.0)

[a]When multiple instruments were used in a single study only one instrument had to satisfy the item in a checklist to have deemed to have met the HRQoL issue for that study.

[b]An issue relating to 'Cultural validity verified' on the checklist has been omitted.

[c]Including three mandatory items; baseline compliance reported, missing data and psychometric properties documented or referenced.

Correlation analysis demonstrated that no confounding variables were present. A linear regression analysis showed the absence of a significant time effect on the MSC scores (β = 0.025; p=0.775). The percentage of studies judged as 'probably robust' was 14.9% for those published between 2005 and 2009 and 13.5% for those published earlier (**Error! Reference source not found.**). A similar pattern was observed in the 'limited' and 'very limited' groups. In fact, the only MSC item that has improved significantly over time was 'rationale for instrument selection'; 36.2% (17/47) of those studies published between 2005 and 2009 compared to 19.2% (17/89) of the studies published earlier provided the rationale.

Quality of reporting on HRQoL was higher in the trials with HRQoL as a primary/co-primary endpoint (**Error! Reference source not found.**). These trials were more likely to report an a priori hypothesis (94.7% vs. 55.6%), the clinical setting in which HRQoL instrument was administered (68.4% vs. 35.9%), and to discuss the clinical implication of the result (89.5% vs. 34.2%). According to the MSC, while 42.1% (8/11) of the studies with HRQoL as a primary/co-primary endpoint were considered 'probably robust', the percentage was much lower for the studies with HRQoL as a secondary endpoint (9.4%, 11/117). Of the studies with HRQoL as a primary/co-primary endpoint, the remaining 57.9% (11/19) of the studies were evaluated as 'limited' with none being 'very limited'. However, 22.2% (26/117) of the studies with HRQoL as a secondary endpoint were 'very limited'.

3.6 Implications of this review

Although HRQoL assessments have the potential to provide a meaningful and clinically relevant outcome of a disease and the effects of pharmacotherapy from the patient's perspective, our analysis reveals that the methodological and reporting rigor of HRQoL assessment in these RCTs has been less rigorous than reporting standards in cancer [53]. Only 14.0% of the studies can be described as 'probably robust'. This compromises the value of such data.

In some studies the researchers did not provide an operational definition of HRQoL and the ambiguity of those constructed has been previously noted [21]. Subsequently, there was no description of how the multidimensional concept of

HRQoL including physical, psychological and social domains was measured. In fact, in some studies the terms “HRQoL” and “physical functioning” and/or “symptoms/side effects” were used interchangeably from study question to methods to discussion. For example, in a study the research question may specifically address only one dimension of HRQoL such as physical functioning but in the discussion the term HRQoL would be used, or a study question may refer to HRQoL but only one dimension of HRQoL such as symptom burden was actually measured. This confusion and ambiguity has been previously reported [54]. Although the summative HRQoL score is influenced by each domain, these domains in isolation do not constitute a comprehensive assessment of HRQoL. Therefore, extreme caution is required in drawing conclusions about HRQoL benefits when the assessment is based on the interpretation of results from a limited number of domains [19]. Furthermore, using a subset of an existing instrument may compromise the integrity of the psychometric properties of the original instrument [55]. Consequently, the use of the term HRQoL should be avoided when the study question only addresses one dimension of the concept or vice versa [54].

In this review, 61.0% of the studies stated an a priori hypothesis (or had predefined HRQoL endpoints) although only 25.0% provided the rationale for the choice of the HRQoL instrument. This is an important issue as an a priori hypothesis and the choice of a specific HRQoL instrument are interwoven [56]. The choice of HRQoL instrument in a study should be determined by the severity and nature of the disease as well as expected benefits and side effects of the treatment. Consequently, the a priori hypothesis should indicate which aspects of HRQoL are measures of interest and likely to be affected by the treatment under consideration [57]. This will ensure that an appropriate, relevant, valid and responsive instrument will be used for the study [58]. By reporting on these conceptual issues, the consumers of research can critically examine the extent to which the selected instrument covers the research question.

Although more than half of the reviewed studies used an existing instrument, only 63.2% of the studies reported psychometric properties or referenced the validation study. This raises a question about the validity, reliability, responsiveness,

sensitivity and appropriateness of the HRQoL outcomes in the remaining studies (36.8%). In addition neglecting to report on psychometric properties of the instrument may also compromise the ability to critique whether the HRQoL instrument is reliable and valid. In this review, 95.6% of the studies documented the timing of HRQoL assessment but only 40.4% of the studies reported on the method of HRQoL instrument administration. These issues are essential in interpreting study data.

In almost half of the studies, the reported duration of the study was 12 weeks (3 months) or less. The timing of assessment is important especially when evaluating an outcome such as HRQoL. In most situations, following a baseline assessment, a sufficient length of time may be required before HRQoL changes occur and this may be different from the time for clinical changes to appear. Incorrect timing of HRQoL assessments could potentially jeopardize the reliability and the validity of the HRQoL findings [59]. Erroneous findings may result due to possible confounding of the treatment effect on HRQoL assessment with the differential effects in assessment timing. If the treatment effect was measured on a HRQoL instrument outside an accepted time window the result may be different. Choosing appropriate timing of HRQoL assessment must be considered carefully to ascertain possible transient effects of treatment on HRQoL.

Only 44.9% of the studies in this review documented missing data and 44.1% reported on baseline compliance. This is an important issue especially in studies of elderly patients with CHF. In such studies, patients often drop out of the study because of severe illness or even death. This may lead to selective loss of information and hence a bias may be introduced. Moreover, the most pertinent HRQoL results could possibly be obtained from patients who may not complete the trial [19]. In addition, this loss of information would reduce the sample size and/or information, hence the ability to detect clinically meaningful differences. Consequently, it is critical to provide information on strategies used to minimize HRQoL missing data and/or at least acknowledge how they were managed to increase validity of HRQoL results. This will aid interpreting HRQoL result.

In this review, few studies with HRQoL as a primary/co-primary endpoint reported sample size based on a HRQoL hypothesis or considered the adequacy of the agreed sample size on HRQoL assessment. In addition, almost half of the studies had a sample size less than 100 patients. All of these studies may have been inadequately powered to detect clinically important differences in HRQoL scores and this was acknowledged in some of the reports. It has been suggested that even when HRQoL assessment is a secondary endpoint and hence a power calculation is not expected, some a priori hypotheses should be made concerning the expected changes in HRQoL scores either as an effect size or minimal important differences for agreed sample size [19]. This assessment will assist in eliminating the disparity between clinical and statistical significance [58].

Most of the studies in this review reported on multiple HRQoL comparisons between different time points or/and using multiple instruments. These can potentially increase the proportion of missing data and false positive results caused by multiple comparisons without appropriate statistical adjustments [60]. Consequently numerous approaches have been suggested to minimize this risk such as comparing only the summary score, adjusting p values, or to analyze only selected domains [19, 60]. However, all of these approaches will place limitations on the interpretation of the results and caution should be exercised in drawing conclusions from such HRQoL results. Furthermore, most of the studies did not specify in the a priori hypothesis whether the comparisons were made between treatment arms after randomization or with their respective baseline scores obtained at randomization. There is clearly a need for the consensus on the most relevant way to analyze longitudinal HRQoL data [56].

In a systematic review [61] of the generic quality of life questionnaire, the Medical Outcome Study Short Form Health Survey, SF-36, the authors concluded that quality of life outcomes in clinical trials are frequently underestimated and often overlooked.

Despite a dearth of information on improving methodological and reporting quality of HRQoL outcomes [19, 62, 63], the reporting quality of HRQoL in CHF

pharmacotherapy RCTs has not improved over time. In this study this trend was noted in all items in MSC checklist except for 'rationale for selecting a specific HRQoL questionnaire'. While few studies published before 2005 addressed this issue the studies published more recently showed higher compliance. This may be due to the US FDA requiring support for the labelling treatment benefit claim when making drug approval decision [64]. As expected, quality of reporting of HRQoL was superior in trials with HRQoL as a primary/co-primary endpoint.

Efforts, especially in oncology, to improve HRQoL assessment and reporting in clinical trials have seen a major improvement [53]. The reasons suggested for this improvement are the development of specific guidelines and checklists for reviewing and facilitating the critical appraisals and interpretation of HRQoL outcomes [65]. A lack of familiarity regarding psychometric considerations of HRQoL measurement issues may contribute to inadequate reporting [53]. Developing and adopting similar guidelines and checklists in CHF may lead to an improvement in reporting.

3.6.1 Limitations of the review

There are some potential limitations to this review. Despite the search strategy using two literature databases, the criteria for this review may have omitted some relevant and important studies especially in non-pharmacological and device trials. However the purpose of the study was to review the methodological and reporting rigor in HRQoL assessment using pharmacotherapy as an exemplar. This review did not take into account unpublished reports and the scarce details in some articles that have limited their usability in this review. Although issues addressed in terms of design and methods of measurement of HRQoL discussed in this review were limited to pharmacological trials, important HRQoL methodological issues in analysis, presenting and interpreting results could be applicable to other RCTs in CHF.

This review did not assess the overall quality of the trial but only the methodological and reporting quality of HRQoL assessment in the trials.

Furthermore, some methodological deficiencies may lie in the reporting (or not reporting) rather than in their performance. In addition, this review did not evaluate the appropriateness or the importance of HRQoL as an outcome in clinical trials or the quality of the validation of the HRQoL instruments used. Although the MSC was developed in oncology, critical HRQoL assessment issues addressed in the checklist were adapted in this review for CHF. Using other criteria, the studies could have been categorized somewhat differently. Furthermore, by summarizing the 11 items in MSC quality criteria into one overall score may have weighted all items as equally important, which may not be the case.

3.7 Chapter summary

This chapter has reviewed the methodological and reporting rigor of HRQoL in RCTs of pharmacotherapy in CHF.

Although HRQoL is an important clinical endpoint with a potential to influence clinical decision making, evidence to date has shown a limited impact of HRQoL on patient management [18]. This may be due to clinicians' skepticism as to the validity of HRQoL. To date few studies reporting HRQoL in CHF were deemed 'probably robust' using validated criteria. It is important to consider that RCTs are perhaps the most rigorous form of research reporting and identify the best case scenario for reporting. Refining guidelines and checklists for the assessment of HRQoL outcomes in CHF clinical trials is warranted and is currently being developed by the Consolidated Standards of Reporting Trials (CONSORT) group [66]. The following chapter will critically review PIOs in CHF across the illness trajectory.

3.8 References

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Chapter 4 Patient Important Outcomes

4.1 Introduction

The previous chapter has assessed methodological and reporting quality of HRQoL in CHF RCTs. The wide variations in methodological and reporting standards have led to difficulties in interpreting HRQoL data which in turn may have led to slow uptake of HRQoL in clinical practice. This thesis conceptually advances the discussion of PROs to discuss the issue of PIOs.

The purpose of this chapter is to review PIO measures used in CHF and discuss methodological issues. The advantages and disadvantages to these outcome measures are included and recommendations for a comprehensive, patient centred outcome assessment suggested.

Outcome measures are important in determining both the efficacy of the treatment and quality of care by capturing patient's health status. Including the patient's perspective via PROs is important but it is often erroneously considered to be the only outcome that is important to patients. Objective measures such as mortality and morbidity in addition to PROs would encapsulate all dimensions of the quality of care and provide more comprehensive account of outcomes important to patients. To describe the PIOs in CHF, a structured literature review was undertaken. This review discusses the concepts and methodological issues related to measurement of PIOs in CHF. Outcome assessment at the level of the patient, provider and health care system is discussed in the context of PIOs. The perspectives of all stakeholders are considered in proposing a core outcomes set that is important to patients but are also meaningful and relevant to providers and health care system. This core outcomes set would potentially provide a comparable, comprehensive and accurate assessment.

As discussed in previous chapters, CHF is a common, complex syndrome occurring most commonly in the elderly [1]. CHF is often associated with limited physical, psychosocial and economic capacity [2, 3]. Symptom burden and lengthy, costly re-hospitalisations are defining characteristics of the CHF trajectory [4]. People with CHF often have multiple medical conditions and live with debilitating symptoms such as fatigue and breathlessness. Therefore, the primary objective in the

management of CHF is to optimise patient's wellbeing in the context of longer-term survival. Balancing these two perspectives is challenging and requires an understanding of the individual's values and wishes, juxtaposed with those of health professionals and society at large.

4.2 Outcomes

Outcome measurement makes an important contribution to describing, interpreting and predicting the effects of disease and the influence of health care interventions [5]. Outcome assessment can be used not only to evaluate the efficacy of interventions but also to describe the impact of care on patients (e.g. patient satisfaction). Furthermore, outcome assessments support evidence-based clinical decision-making at the individual patient level, and identify aspects of care for further improvement [6]. Consequently the concept of outcomes naturally directs attention to the needs of patients and their well-being [7].

Choosing inappropriate outcome measures may lead to unimportant or misleading information, wasted resources and a loss of opportunity to demonstrate potential benefits. Despite debate on perspectives of management in CHF [8-11], choosing which outcomes to measure from the large range available remains challenging, and researchers and clinicians alike require further guidance [12]. At the same time, as mentioned in previous chapters, there are calls from agencies such as the FDA in the US [13] for researchers to generate outcome models that clearly explain the roles and relationships between outcomes in providing an evidence base. As individuals live longer with chronic conditions, the burden from comorbidities increase and assessing the relative contributions of different conditions and treatments becomes increasingly complex [14].

4.2.1 Patient important outcomes

A growing interest in patient centred care has naturally led to seeking outcome measures that are important to patients[14]. Outcomes that are important to patients are those that patients notice, care about and for which they would be willing to undergo a treatment with associated risk, cost, or inconvenience for it to be the only thing that changed [15].

PIOs are outcomes that directly measures patients' QoL [16] and/or quantity. This is in contrast to surrogate, substitute, or physiologic outcomes that clinicians may consider important. Intermediate measures such as medication adherence and surrogate outcomes such as improved cardiac output may be easier and quicker to measure. However these outcomes are not important to patients as they carry no meaning in improving the quality or quantity of life [17]. In contrast, outcomes such as symptoms, mortality and morbidity/hospitalisation would be valued. Clinicians and health service managers, planners and policy makers often need intermediate and surrogate measures to monitor progress, understand causal relationships and evaluate cost-effectiveness. Yet, the quality of these measures ultimately hinges on the strength and validity of the evidence that they are predictive of outcomes that are important to patients. Other terms used to indicate patient important outcomes include "patient oriented outcome" [18], "personal significant outcome" [19], "patient centred outcome" [20] and "patient focused outcome" [21].

4.3 Information sources and search

Electronic databases Medline and Cumulative Index to Nursing & Allied Health Literature (CINAHL) were searched in addition to the World Wide Web using the Google Search Engine. Medical Subject Heading (MeSH) terms and keywords used in this search related to CHF and outcome assessment, outcome classification, health care outcomes and patient outcomes (see Appendix). Searches were not limited to any date range to enable insights into changes that may have occurred in outcome concepts or methods. Further additional data sources, such as clinical guidelines and policies were hand searched for information relevant to the review. The search was limited to reviews, editorials or comments on outcomes in CHF published in English. Methodological issues pertaining to adverse events [22] and burden of disease (e.g. frequency of tests, clinician assessment of disease burden) [23] were also identified.

4.3.1 Data extraction and synthesis

Data were summarised and managed using Endnote XV (Thomson Reuters, New York) software. Articles retrieved were analysed for discrete outcome measures

identified as important to patients and to discuss issues in methodological assessment and their relevance to patients. In addition those outcomes identified to be important to patients were analysed for their relevance to clinicians and health care systems.

4.3.2 Eligibility criteria

Articles were eligible if they identified outcomes important to patients in CHF and considered concepts and methodological issues related to measurement of these outcomes in CHF.

The following questions drove the selection of articles and information.

- What are the discrete outcomes measures identified as important to patients in CHF?
- What are the measurement and methodological issues of outcome measures that have been identified as important to patients?

4.4 Results

The following numbers of references were retrieved for this review. CHF and outcome assessment (n=107), outcome classification (n=2), health care outcomes (n=4), and patient outcomes (n=65) (see Appendix).

4.4.1 What are the discrete outcome measures identified as important to patients in CHF?

Discrete outcome measures identified as being important to patients were; survival (mortality) [8, 9, 24-26], event free survival [24, 27, 28], hospitalisation[8, 9, 11, 20, 29], PROs (e.g. symptoms, QoL) [9, 10, 24, 30, 31], and economic outcomes (e.g. cost and resource use per patient)[23, 32-34]. In addition, outcome measures such as mortality, morbidity as well as PROs such as symptom burden, functional status, psychological state, compliance with a therapeutic regimen, self-management and QoL are identified by the American College of Cardiology/American Heart Association (ACC/AHA) as important data elements for assessing the clinical management and outcome of patients with CHF [20]. To simplify understanding of

discrete outcome measures in CHF, the distinction between clinical trials and management has been made in their discussion.

Mortality

Mortality is a critical outcome measure in CHF especially when it is unexpected, premature, or avoidable. Unexpected death may be a result of both cardiac and non-cardiac causes. To be a reliable and valid outcome at the system level, appropriate casemix and severity adjustments need to be made to adjust for these differences [25].

In CHF clinical trials, all-cause mortality has found favour as an unbiased and unambiguous outcome [9] and has been used as a sole primary outcome [8]. However as CHF care improves, mortality is becoming a less frequent event in some clinical trials, with the result that large sample sizes are required to detect differences between intervention and control groups [9]. This has led to mortality being included as part of a composite outcome (usually with hospitalisation). This is controversial because of the potential for unequal weighting of events [24].

The choice of all-cause versus cause-specific mortality is also contested [26]. Although all-cause mortality will result in a higher event rate, the inclusion of deaths not the result of cardiovascular disease will invariably reduce sensitivity and therefore power to detect an intervention effect [26]. Assessment of cause-specific mortality improves precision but presupposes no impact on non-cause specific mortality, which may not necessarily be true.

As well as providing a clearer indication of the effects of management, cause-specific mortality can also provide insights into a broader concept of chronic condition and its mechanism. However, a focus on cause-specific mortality requires researchers to distinguish between cardiovascular death and death caused by comorbidity. The difficulty of adjudicating the cause of death may depend on the quality of documentation provided on the death certificate, particularly for community based deaths [26]. Furthermore, although cause-specific mortality may provide clinicians and health service operatives with important information to

improve care and service delivery, it may not be meaningful to patients or their families for whom the impacts will be the same regardless of cause [26].

Hospitalization

Data on hospitalization (eg. cause of admission, length of stay) provides useful information on prognosis, allows inference regarding the burden of CHF and management on patients and their families, and informs cost effectiveness analysis [24]. Despite its utility, hospitalisation as an outcome measure has limitations. Admission to the hospital is influenced by patient and social preference and differences in practice patterns, with thresholds determining admission and length of stay varying according to country, region and even institution [8]. The use of "observational stays" in some institutions and "short stay"[8] holding units in emergency departments further confounds comparison between studies. As with mortality, there is also the dilemma of whether to choose all-cause or cause-specific hospitalisation, with advantages and disadvantages to each [26]. When adjudicating the reason for hospitalisation, the definition of CHF hospitalisation is likely to vary depending on severity of CHF, comorbidities and related admission policies [11]. Although the rigor of this metric has been widely challenged, the importance of hospitalisation in terms of health care system costs has maintained this focus.

Patient Reported Outcomes

As discussed previously, over the past two decades there has been a growing interest in collecting outcomes that are important to patients to ensure clinical care is patient centred [35]. Implicit in this process is obtaining the perspective of the patient through the use of PRO.

As discussed in previous Chapters, PROs can be used to inform health decisions in a wide range of applications from individual patient decision-making through to developing health policy aimed at improving population health [36]. Routine administration of questionnaires to measure PROs can be used to screen for unmet needs [7] or problems such as depression and anxiety [37]. Evaluating satisfaction with treatment may assist providers in understanding the issues influencing

treatment adherence and may help identify aspects of management linked to long-term treatment outcomes [38]. PROs can also facilitate communication amongst the health care team by providing a common language amongst professions from different clinical backgrounds [39]. Finally, established discrepancies between clinician and patient perceptions of symptoms and treatment effectiveness mandate collection of patient reported data to inform future practice [39].

In clinical trials, PROs provide a number of advantages over and above traditional outcomes such as mortality. They offer a way to differentiate benefits when two or more treatments present with similar clinical efficacy [40]; they measure the benefit of "add-on" therapy that has the primary objective of providing an incremental benefit to QoL rather than substantial impact on survival [41]; and they can be used to examine long-term impacts of treatment on daily life in the context of lengthy survival, increasingly an issue in CHF [42].

Issues in Patient Reported Outcomes

PROS usually reflect unobserved (latent) concepts which may manifest themselves in different observable ways depending on the condition or treatment of interest. There is a challenge in selecting the most appropriate measure that would fulfil the objectives of the outcome assessment. It must also be guided by the severity and nature of CHF and ensure PROs measure selected would measure benefits/side effects of the therapy as well as the change in patients as CHF progresses. PROs are inherently subjective and rely on patient's self-report [43]. This means it is also imperative for PROs to be reliable and valid as well as responsive and relevant [44]. In addition, relying on self-report means PROs data are more prone to missing data than other clinical outcomes [34]. This is an important issue especially in many CHF studies where elderly patients may often drop out due to severe illness or even death. Consequently, this type of missing data may lead to bias which may result in an erroneous conclusion [45].

In evaluating PROs, the timing of the outcome assessment is crucial. In most situations, the timing of the assessment of PROs will depend on disease progression, the therapy response, the risk of premature death or adverse events

and the respondent burden [44]. Incorrect timing of PROs assessments could potentially jeopardize the reliability and the validity of the PROs findings [46] by biasing the treatment effect. If an evaluation of PRO measure took place outside an accepted time window the result may be different. In addition, choosing appropriate timing of PRO assessment, requires careful consideration of the transient effect of therapy on PROs measure.

PRO data, especially QoL, comprise multiple components such as individual's perceived physical, psychological, and social well-being [47]. Statistical analyses of these data often result in false significant results due to multiple testing. Several methods have been suggested to address the multiplicity issues such as comparing only the summary score, adjusting p-values, or to analyze only selected domains [45, 47].

In interpreting PROs, there is a need to determine the minimal important difference (MID). This measure enables interpretation of outcome assessment beyond statistical significance. However, it can be argued a meaningful change is a subjective concept and it may differ depending on different perspective. There is clearly a need for a comprehensive interpretation strategy that incorporates different anchors, each having its own metric that is meaningful to a given audience [32]. Works have been carried out to establish MID for Minnesota Living With Heart Failure Questionnaire [48] and the Kansas City Cardiomyopathy Questionnaire [49], two most popular HRQoL measures used in CHF [50].

Economic Cost

With two-thirds of the economic burden of CHF accounted for by admissions to hospital [34], outcomes such as admission or/and readmission along with visits to the physicians are considered important [32]. Currently CHF patients have three times as many visits to the health care provider, twice the number of emergency visits and greater than three times more inpatient admission compared with other patients [51]. Subsequently, frequent admissions to hospital and visits to physicians would have an impact on the economic cost. At an individual level, economic cost

would include lost productivity as well as direct and indirect costs of care at personal level such as hospital transportation [33]

Adverse Events

An adverse event is defined as an unintended harm due to medical management or lack thereof in contrast to complication arising from the underlying disease [22]. Although adverse events may be linked with quality of care and patient safety, presence does not necessarily indicate poor quality, nor their absence good quality [22]. Most patients with CHF have one or more co-morbid condition that will potentially cause treatment conflict, [52] especially when multiple medicines are prescribed. This places patients with CHF at risk of adverse outcomes which may be captured by mortality, hospitalisation and PROs (eg. side effects and symptoms).

Burden of disease

Burden refers to the demands experienced by patients, caregivers, clinicians, the health care system and society [5]. Patients' and carers' burden can be expressed as mortality, hospitalisation, and PROs such as symptom burden [31]. In some instances economic burden is also described at an individual level. As mentioned above, this may include lost productivity as well as direct and indirect costs of care such as hospital transportation due to [33] but may also include physical and emotional burden especially for the elderly. Patients' and carers' burdens are usually linked with expectations of and satisfaction with care [5] as measured via PROs.

The burden of CHF at a system level has generally been measured with traditional indices such as incidence, mortality, and morbidity and increasingly health services utilisation, particularly hospitalisations [53] and they may provide valuable information to patients. One definition of the burden of disease is a measure of the years of healthy life that an individual or population loses as the result of disease. Generic outcomes that combine both mortality and morbidity into a single index such as disability adjusted life years have also been used [54]. However from patient's perspective these indices are not easy as easy to understand. Identifying

the outcomes important to patients such as QoL are important considerations in determining disease burden.

4.4.2 Outcome assessment in clinical management

In clinical management, the purposes of outcome measurement typically include monitoring and support of patient progress, diagnosis, treatment and communication [55]. Outcomes assessment in clinical management can be targeted at either or both of two levels: at an individual patient care level and/or at an aggregated system level [56]. Information at the system level can be collected and analysed at either the clinic or group practice level.

In clinical management, outcome assessments typically use routine data to avoid undue burden on patients that may not have immediate consequences for their own personal care. Routine outcome data is subject to numerous biases and is unlikely to be of sufficient quality for rigorous evaluation of treatment efficacy [57]. Nonetheless, outcome data can be utilised in measuring the quality of care, designing system interventions, reallocating resources and research efforts, training health care personnel and characterising a patient population to better understand their needs.

4.5 Discussion

The current review has found a range of commentaries and reviews concerning outcomes measures important to patients in CHF yet no gold standard exists. While there was a general agreement that outcomes assessment is essential in improving care, a number of strengths and limitations were highlighted in each of outcome measures important to patients.

Outcomes in CHF are used to describe the impact of treatment/care on patients' lives. Incorporating patients' perspective in the form of PROs means an essential element [58] of patient centred care is being practiced. Indeed, there has been a call to include PROs in routine clinical practice [41]. Therefore, choosing outcome measures that are meaningful to patients is essential. Traditionally patient outcomes in CHF have been mortality, hospitalisation and avoiding or decreasing

adverse events of care [10]. With debilitating symptoms including fatigue and breathlessness, improving functional status and HRQoL have become patient important outcomes. Increasingly patients' perspective as expressed in PROs such as HRQoL, functionality, symptoms (and symptom management) and more recently quality of death have become outcomes important to patients [59].

Increasingly, there is a recognition that patients' desired outcomes may change as the patients and their carers evolve as the disease progresses and treatment/care becomes familiar [60]. Undoubtedly, for many patients, outcomes such as mortality and morbidity/hospitalisation would play a central role and override any consideration for other outcomes. This would be the case, especially in patients with mild symptoms where their prime objective would be to improve survival [61]. However in more severely ill patients with distressing and in times disabling symptoms, this may not be so; an improvement in their QoL or symptom relief may be more important [62]. Consequently, in examining PIOs, PROs need to be considered in conjunction to clinical outcomes such as mortality and morbidity/hospitalisation [63]. In order to consider the relevance and meaningfulness of these measures, it is useful to consider patient, clinician and system perspectives in CHF outcome assessment and these are summarized in.Table 4.1.

4.5.1 Clinician level

In providing care to patients with CHF, clinicians aim to increase survival and improve QoL both by managing current problems and preventing future morbidity. To achieve this, clinicians need to monitor the processes and results of care to inform future improvements to care and support shared decision-making with patients [64]. Process measures include patient understanding of self-management advice, availability of support and adherence to treatment as well as vital signs, laboratory and diagnostic test results, and response to medications [12].

Physiological and elemental outcomes such as changes in pulmonary capillary wedge pressure and natriuretic peptide levels may be disease rather than patient-centred but are nonetheless an important part of CHF patient management [65].

They inform clinicians of the status of disease process as well as the mechanism related to the patient problem and a better understanding of the way a treatment works [65]. Intermediate outcomes should ideally require minimal additional resources and minimal disruption to the delivery of care. Furthermore, they should be clinically useful and acceptable to patients [56]. As much as possible, they should inform concrete action (eg. provision of information) [63] to improve patient care. But it is important to emphasise that these outcomes should be supportive of, rather than alternative to outcomes that are important to patients.

4.5.2 System level

At a system level, outcomes evaluate changes in health of a defined population as a result of health care or health system activity [66]. Outcome measures at this level assist in establishing and evaluating health policies that may benefit CHF communities. Such methods of assessment are critical in informing policy decisions. As demands on resources increase, outcome measures are increasingly needed to enable disparities in burden to be highlighted across different health conditions and geographical regions as well as over time. Outcome measures have an important part to play in examining accessibility of quality CHF care across the population. These applications are needed to ensure the health care system is suitably responsive to the needs of different groups.

Table 4.1 Patient, clinician and system perspectives in chronic heart failure outcome assessment

	Perspective		
	Patient	**Clinician**	**System**
Reason for interest in outcomes	• Minimize risk of CHF • Restore to "health" in timely way • Ability to live a normal life	• Assess patient needs • Provide appropriate care/treatment • Monitor quality of care/ treatment provided	• Plan services • Monitor the quality of care/treatment provided • Justify cost of care • Improve population health • Reduce health disparities
Desired outcomes	• Timely access to quality care • Minimize symptom burden and 'functional limitation • Survival • Avoid major clinical events such as hospitalization • Self- management of CHF • Feel safe and secure and satisfied with care	• Patient adherence/satisfaction • Improved self-management of CHF • Appropriateness of treatment/care provided • Avoid adverse events • Good liaison with other health care team	• Reduce incidence/prevalence of CHF • Appropriate service provision • Improved knowledge and understanding of CHF and related risks. • Population based surveillance system
Possible outcome measures	• Mortality • QOL • (Re)hospitalization • Functional status • Patient satisfaction	• Mortality • Symptoms (eg. dyspnea) • LVEF • Patient satisfaction	• Mortality • Incidence/prevalence • Hospital days • Cost of treatments • Workforce implications

Given the escalating health care cost associated with CHF and other chronic conditions, it is important to balance societal benefits with expenditure to allocate care and resources judiciously. There is a need to understand the relative benefits of the various treatment options for CHF in terms of clinical and economic outcomes. The quality adjusted life year (QALY) is widely used for economic evaluation across health care [67]. QALYs combine information on both quantity and quality of life and offer a standard unit for comparison across different interventions and places on the disease trajectory [68]. That said, there have been numerous criticisms of QALYs, especially concerning the methods used to generate their utility weights and the use of QALYs for informing allocation of health care funds between disparate conditions [30]. A broader assessment at system level would include cost-benefit analyses [69] and loss of productivity as possible societal outcomes.

Two-thirds of the economic burden of CHF can be accounted for by admissions to hospital alone [34], making interventions that avoid (re)admission a priority from the system perspective. At the same time, there is a need to measure hospitalisation and other system outcomes in terms of their impact on the patient [70]. While we may assume that patients generally wish to avoid hospitalisation, it may be that this is a preferred outcome for some people who lack support in the community [71]. PROs such as psychological wellbeing, unmet needs and satisfaction with care have so far had a limited influence at the systems level. Future work is needed to integrate these measurements into the systems level model.

4.5.3 Moving towards a prioritised, integrative model of outcomes assessment

This chapter has considered outcome measures of importance to patients and considered their importance at clinician and health care systems level. Mortality, hospitalisation and PROs are outcomes that are relevant and important to all stakeholders of CHF care and have wide application in research and clinical practice. The outcomes are important as it facilitates decision making at all levels of care. To patients and healthcare purchasers outcome measures will provide information

about the quality of care available to them; to clinicians and healthcare systems a feedback on the quality of care that they provide, which in turn will enable them to identify areas for improvements as well as differentiate themselves from other institution [70]. If standardised, this "core set" of outcomes has potential to enable both evaluation of health care effectiveness and monitoring of population health [72].

Identifying consensus in the relevance, appropriateness and importance of outcomes between patients, providers and health systems is important in generating an integrative model of health care assessment that has utility and relevance. This will require a reengineering of health care systems to shift the rhetoric of person-centred care to conceptual integration and relevance in systems and processes. Shifting beyond tokenistic consumer representation will be important [73] .

Furthermore, as evaluation metric are often a driver of service organisation and delivery, having a genuinely patient centred outcome goal is likely to alter service provision. The critical issue is whether this should be approached by developing a single measure, by measuring a core set of outcomes and trying to combine the results as a composite outcome, or by keeping them as a set of individual outcomes. Although there is an argument any single outcome may not be adequate to capture important differences [68], comparability and interpretability of outcome assessment will be greatly facilitated by a simple measure of outcome [74] such as a composite outcome. In addition, combining multiple outcomes into a single summary measure is a useful approach for defining 'net benefit' [75].

4.6 Chapter Summary

Although the literature challenges conceptual and methodological assumptions of conventional end-point assessment methods, to date there has been limited application on non-traditional measures [24]. Choosing measures must depend on the capacity to provide comprehensive, comparable, meaningful, and accurate reflection of outcomes as well as the capacity for data collection. Measurement issues such as reliability, validity and utility in meeting the needs of a range of

stakeholders are important but ensuring these outcomes are important to patients is as or more important. This requires a conceptual shift that requires an extension from PROs to PIOs. For example, for many patients with CHF, mortality is of a critical consideration. This is illustrated in the high uptake of left ventricular device as destination therapy in the US [76].

While it is likely that utility will vary from the perspective of patient, clinician and health care system, the needs of clinicians and the system should be seen as supportive of rather than alternative to those important to patients; a core outcomes set with broad-scale application and appeal.

A strategy to encapsulate the range of perspectives as outlined in this chapter has been the use of composite outcomes. The next chapter will discuss methodological and weighting issues in composite outcomes combining set of patient important outcome measures identified in this Chapter; namely, mortality, hospitalisation and PROs.

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Chapter 5 Assessment of performance of composite outcomes

5.1 Introduction

As discussed in previous chapters, CHF is a common, complex and multifaceted syndrome [1]. Living with a life limiting illness challenges traditional outcomes such as mortality and morbidity in clinical trials to assess the impact of CHF and treatment options on patient centred outcomes particularly QoL. Studies using comparative normative data the degree of physical, mental and social functioning impairment was greater in patients with CHF than those with other chronic diseases [2, 3]. Many patients with advanced heart failure ascribe greater importance to quality than to duration of life [4]. Subsequently, selection of outcomes in both clinical trials and practices should be undertaken with great care.

In Chapter 4, outcome measures important to patients were determined and their usefulness at provider and health care systems level were considered. Mortality, hospitalisation and PROs, such as QoL were proposed as a core outcomes set relevant and important to all stakeholders of CHF care and explored their wide application in research and clinical practice. This Chapter will discuss the strengths and weaknesses of composite outcome assessment and proceed to test three established composite outcome models which incorporate a core outcomes set of mortality, hospitalisation and an example of PROs, QoL [5-7].

Beyond conceptual discussion, measurement issues were described through undertaking a secondary analysis of a prospective, multi-centred RCT of 280 hospitalized CHF patients in the Which Heart failure Intervention is most Cost-effective & Consumer Friendly in Reducing Hospital Care? (WHICH(?)) Trial [8]. These data were used to compare and contrast three composite outcomes that comprise mortality, hospitalisation and QoL in CHF to understand the influence of each component to the final outcome.

5.2 Outcome measurement in clinical trials

Exploring different outcomes in CHF and cardiovascular clinical trials have demonstrated the lack of consensus on appropriate measures [9-11]. In some CHF clinical trials, there is a recognition that treatment efficacy needs to be measured by multiple outcomes, especially where management or the outcomes of

interventions have multiple components [12]. A composite outcome in a clinical trial is where clinically relevant outcomes are combined into a single outcome that can characterize clinically meaningful benefits of a treatment [13].

5.3 Composite outcome

Essentially there are three types of composite outcomes. The first type is a total score which effectively combines signs and symptoms of a disease [14]. The second type of composite outcome is an 'event' rate after a certain period has elapsed since treatment [14]. The third type of composite outcome is defined as the time to the first 'event'. In both the second and third type of composite outcomes the definition of 'event' is pre-specified clinically relevant and meaningful event amongst several possible event types [14].

5.3.1 Issues in composite outcome

Using a composite outcome requires considerations, such as the selection of the number and type of clinical relevant components, to include in a composite as well as the interpretability of such an outcome [11]. The number of components in a composite outcome and their relative weightings have important implications in the interpretation of the composite outcome [11]. In CHF trials, the composite of mortality and hospitalization has become the standard primary outcome for regulatory trials [17] with or without worsening HF. The strengths and weaknesses of such an approach have been widely debated and discussed [13].

5.3.2 Strength of composite outcome

Composite outcomes are useful both for capturing multiple components and additive effects of interventions and also for reducing sample size due to increased event capture. These approaches to outcome assessment are usually considered when no single end point can accurately capture the totality of the patient experience [15]. The benefits of such an approach include a reduced sample size and cost of undertaking a trial, and the ability to capture the net benefit of the intervention [16]. These benefits have led to increased use of composite outcomes in clinical trials.

Combining multiple outcomes into a single summary measure will undoubtedly define 'net benefit' [16]. Using a composite outcome will circumvent the need to make an allocation for multiple hypotheses testing, as one is essentially dealing with a single outcome [14, 17]. In addition, the problem of competing risks can be avoided especially if a clinical outcome such as mortality, is combined with morbidity [15]. Ultimately, the composite outcome derived from mortality, hospitalisation and QOL would lead to greater efficiency and higher quality of care by incorporating the clinical effectiveness at the individual patient level and economic costs as expressed in hospitalisation at the population or policy level.

5.3.3 Weakness of composite outcomes

Composite outcomes are difficult to interpret when the treatment effects vary considerably across the components of the measure. The most extreme case would be when the components are moving in different directions such as an increase in mortality and an improvement in QoL. The problem of interpretation is compounded when components are dissimilar in patient importance [18]. Many of these problems may be resolved by choosing clinically relevant components of the composite and applying appropriate weightings of these components [11, 18]. Yet there is limited discussion on the selection of components as well as derivation method of composite outcomes or in establishing the standards for weighting components of a composite outcome.

5.4 Objective

The study presented in this chapter was designed to provide a better understanding of measurement issues in composite outcome assessment. Examples of composite outcomes incorporating mortality, hospitalisation and QoL in CHF management were examined in data derived from a pragmatic trial comparing multidisciplinary CHF management delivered via an outreach, home-based intervention (HBI) or outpatient, specialised CHF clinic-based intervention (CBI) [8]. Three commonly known composite outcome models were selected. These are Packer's ordinal composite score (improved, unchanged or worse)[6], Cleland's Patient Journey [5] and composite outcome used in the African American Heart Failure Trial (A-HeFT) [7]. Each of these composite outcomes incorporates all-cause mortality,

hospitalisation and QoL albeit using different derivation method and/or different weighting of the components.

The main objective of this analysis was to compare these three composite outcomes to increase the understanding of the numerous pathways that components influence the final outcome in CHF patients. Specifically, three composite outcomes were compared and contrasted using the same data from a prospective trial of community CHF management [8]. The rationale for the choice of this data set was to capture the perspective of living with CHF. Moreover, this data set was more likely to have captured the perspective of the 'real' world of CHF, rather than a highly selected clinical trial population [19].

All components in the composite were examined separately to estimate their relative effect on respective composite outcome. An association between each component (ie. mortality, hospitalisation and QoL) to their respective composite outcomes will be examined.

This analysis did not seek to assess which composite outcome is the 'best' nor to assess the validity of these composite outcomes but rather to try to gain insight into the relationship among composite outcomes that measures similar component, namely mortality, hospitalisation and QoL. In addition, using Packer's score [6], the Patient Journey [5] and A-HeFT composite outcome [7] we sought to examine the methodological consequence of each component on the final outcomes.

5.4.1 Packer's composite outcome

The Packer's composite outcome was first introduced by Packer in 2001[6]. This score combines mortality, heart failure hospitalisation, change in NYHA classification and a change in patient's global self-assessment of QoL, to classify patient as improved, unchanged, or worsened (Table 5.1.) Amongst three composite outcomes examined in this study, this composite outcome is perhaps most widely used in clinical trials. The Packer score has been used in the predictors of response to cardiac resynchronisation (PROSPECT) study[20], and the resynchronisation reverses remodelling in systolic left ventricular dysfunction (REVERSE)[21] to name a few (Table 5.1).

Table 5.1 Packer's composite, Patent Journey, and A-HeFT composite

Component	Packer's composite	Patient Journey	A-HeFT composite
Mortality	All-cause mortality expressed as an indicator variable (N=0, Y=1)	Days dead: The number of days from all-cause mortality to the end of study.	All-cause mortality expressed as an indicator variable (N=0, Y=1)
Hospitalisation	First HF Hospitalisation expressed as an indicator variable (N=0, Y=1)	Days in hospital: Total time in hospital for all causes Add the durations of all individual hospital stay	First HF Hospitalisation expressed as an indicator variable (N=0, Y=1)
Quality of Life	Change in patient global assessment and change in NYHA functional class	Average NYHA functional class over the duration of the study moderated by the increased use of diuretics	Change in MLWHFQ from baseline to follow-up.
Derivation method	Patients are classified as worse, same or better as:	Initially, Days Alive and Out of Hospital (DAOH) will be calculated. The patient journey	This composite outcome consists of composite score of weighted values of all-cause mortality, first

Component	Packer's composite	Patient Journey	A-HeFT composite

	Worse
	Experienced death or HF hospitalisation during the planned duration of treatment or reported worsening of their NYHA class* or global assessment by at least one class at the final visit compared to the baseline.
	Same
	Neither improved nor worse (ie. Did not experience death or HF hospitalisation and no change in patient global assessment of QoL or NYHA class)
	Better
	Experienced a ***favorable change*** in NYHA class or in the patient global
		incorporated a patient's functional status by allocating each day of the DAOH to the last known NYHA status of the patient for that day.
		Calculation of DAOH:
		Total days in the study: number of days from randomization until the date of the final patient examination (if alive) or end of study.
		DAOH = Total days in the study – (days dead + days in hospital)
		Apply the following score weightings as reported in the COMET trial to the various
			HF hospitalisation and change in QoL score using MLWHFQ.
			Scoring scheme
			• All cause death (at any time during the trial) (-3 points)
			• First (HF) hospitalisation (adjudicated) (-1 point)
			• Change in quality of life
			  • Improvement by 10 units or more (2 points)
			  • Improvement by 5-9 units (1 point)
			  • Change by <5 units (0 point)
			  • Worsening by 5-9 units (-1 point)
			  • Worsening by 10 units or more (-2 points)

Component	Packer's composite	Patient Journey		A-HeFT composite
	assessment by at least one class from the baseline but did not experience death or HF hospitalisation during the course of the trial.	categories NYHA class I II III IV	 Weight 1.00 0.86 0.76 0.60	
Final Outcome	An ordinal outcome of • Worse • Same • Better	0 - Total Potential follow up days		-6 to 2

5.4.2 Patient Journey

The Patient Journey is another composite outcome in CHF that incorporates information on mortality, hospitalisation and QoL. It also includes the change in therapy in the scoring scheme in this composite outcome [5]. Essentially this measure is a refinement of days alive and out of hospital (DAOH). It incorporates longevity and out of hospitalisation into a single measure in days, and weighting them using the patient's QoL as measured with the question "How have you been feeling over the past week?" with a five-point scale from very good to very poor [5]. This five point score is then converted to a value between 0 and 1 which subsequently is applied to DAOH (Table 5.1). The intensification of diuretic therapy to control symptoms is also integrated by assuming patients to be one class worse in the patient QoL than actually expressed, unless the patient is already in the worst class [5]. In this metric a reduction in diuretic therapy is not considered to have led to improvement in QoL.

5.4.3 African American Heart Failure Trial composite outcome

The A-HeFT composite outcome is designed to consider all-cause mortality, a first HF hospitalisation, and a change in QoL using MLWHFQ. A weight given to each component to generate the composite is shown in Table 5.1. Initial score assigned to all patients is 0, which will change depending on patient's experience; death at any time, counted as -3, a first hospitalization from HF -1 and a change in QoL varying from -2 to 2 depending on the degree of improvement or worsening of QoL (Table 5.1). This composite outcome only considers the event of the first HF hospitalisation and not the total number of HF hospitalisations. Hence the A-HeFT composite outcome focuses on the change from baseline status rather than an absolute number of events [7]. Interestingly, this composite outcome assigns greater values for some changes in QoL than for first HF hospitalisation.

5.4.4 Scoring

The scoring algorithms for each of the components for the composite outcomes are summarised in Table 5.1. Each component was considered alongside the most comparable components. Despite comparable components measure similar

concepts they capture and score them differently. This was especially evident in Patient's Journey, which is weighted DAOH, hence the final outcome is in days. The first step in the Packer's score and A-HeFT composite is to express death and first HF hospitalisation information as an indicator variable (0, 1). The extent of difference in measuring and scoring scheme for each component are apparent even in hospitalisation component; for Packer's and A-HeFT score, component to be incorporated was HF hospitalisation whereas for Patient Journey, it was all cause hospitalisation. For QoL component, not all composite outcomes use the same instruments and in some cases more than one measure are used to capture QoL. In Packer's composite score, change in NYHA functional class is combined with information on the changes in patient's QoL, while in Patient's Journey, information on increased use in diuretic is used to adjust QoL weights to be applied to DAOH.

5.5 Method

Data used in this study came from the WHICH(?) a multicentre RCT [8]. Briefly a detailed description of the rationale and design, baseline findings and primary results is provided [8, 22].

The main focus of the study was to compare the multidisciplinary CHF management delivered via an outreach, HBI with an outpatient or a CHF specialised CBI. The inclusion criteria included the moderate to severe symptoms of HF with NYHA functional class II-III with at least one admission for acute heart failure. A total of 280 patients were recruited from three tertiary referral hospitals in three different states in Australia.

5.5.1 Study Data

Detailed demographic and clinical data were collected at baseline (see Table 5.2 for indicative profiling in a standardized manner by trained personnel). All surviving patients were subject to clinical follow-up at 6 months (brief telephone call), 12 months and a final follow-up up to 18 months (pre-scheduled home or clinic visit).

5.5.2 Post-Discharge Management

The key components and principles of post-discharge management of CHF, either delivered as an outreach, HBI or via a CBI coordinated via a specialist CHF

outpatient clinic, according to best practice guidelines. The Australian health care system provides universal health care for the population with only minimal costs (capped for those with chronic disease) for hospital treatment, pharmacotherapy and community care (including family physicians). The study was designed to standardize the elements of care (often supported by the same cardiologists and general practitioners).

5.5.3 Study Design

Briefly, HBI patients were scheduled to receive a home visit by a trained CHF nurse within 7-14 days of hospital discharge. This comprised a structured and detailed assessment of the patient's clinical stability, application of gold-standard pharmacological and non-pharmacological management and any factors likely to positively or negatively impact future health outcomes. Subsequently, a report was sent to the patient's family physician and cardiologist and planned management (including telephone follow-up, referral to other health care professionals and additional home visits) was arranged. Regardless of initial assessment, those discharged to home following an unplanned hospitalization were subject to re-evaluation of the relative success/failure of management by the CHF nurse. Similarly, CBI patients were scheduled to attend a post-discharge visit to the nurse-led specialist CHF clinic where they had access to a multidisciplinary team. The same principles of assessment and follow-up as per HBI were applied. The key differences being that for the CBI group: a) management was primarily directed through the specialist CHF clinic on an outpatient basis and b) they did not receive a comprehensive home visit. No restrictions on access to other health care services were applied.

5.5.4 Baseline characteristics

Of these, 143 patients were randomized to the home-based and 137 to clinic-based post-discharge management. As previously described [8], baseline characteristics were similar in the 2 groups. All hospitalisations were adjudicated on the type (elective/unplanned) and the causes and all death were reviewed by a blinded outcome committee.

Table 5.2. Baseline characteristics according to study assignment (n=280)

	All ***n=280***	***HBI*** ***n=143***	***CBI*** ***n=137***	***p-value***
Demographic Profile				
Men	*203 (73)*	*104 (73)*	*99 (72)*	*p=0.931*
Age at entry (years)	*71 ± 14*	*70 ± 15*	*73 ± 13*	***p=0.046***
Living alone	*155 (55)*	*80 (56)*	*75 (55)*	*p=0.746*
Less than 12 years education	*54 (19)*	*32 (22)*	*22 (16)*	*p=0.520*
Risk Factor Profile				
Hypertension	*177 (63)*	*93 (65)*	*84 (61)*	*p=0.519*
History of Smoking	*194 (69)*	*97 (68)*	*97 (71)*	*p=0.590*
BMI (kg/m^2)	*28.3 ± 6.9*	*28.6 ± 7.8*	*28.0 ± 5.8*	*p=0.537*
Total cholesterol (mmol/L)	*3.9 ± 1.3*	*4.0 ± 1.3*	*3.9 ± 1.3*	*p=0.765*
Type 2 diabetes mellitus	*109 (39)*	*51 (36)*	*58 (42)*	*p=0.252*
CHF profile				
Months since CHF diagnosis	*39.6 ± 63.7*	*34.6 ± 55.3*	*44.8 ± 71.0*	*p=0.200*
LVEF	*30.1 ± 9.2*	*30.2 ± 9.8*	*30.0 ± 8.4*	*p=0.865*
Preserved LV function	*75 (27)*	*35 (24)*	*40 (29)*	*p=0.534*
NYHA Class II/III	*238 (85)*	*118 (83)*	*120 (88)*	*p=0.235*
Ischaemic cardiomyopathy	*159 (57)*	*78 (55)*	*81 (59)*	*p=0.257*
Prior CHF admission (1 year)	*162 (58)*	*85 (59)*	*77 (56)*	*p=0.584*
Index Admission				
Principal diagnosis of CHF	*185 (66)*	*101 (71)*	*84 (61)*	*p=0.100*
Length of stay (days)	*8.9 ± 7.8*	*8.2 ± 7.4*	*9.5 ± 8.1*	*p=0.169*
Coronary care unit (days)	*4.9 ± 7.0*	*5.4 ± 7.3*	*4.4 ± 6.6*	*p=0.419*
Clinical Profile				
Acute heart failure	*134 (48)*	*69 (48)*	*65 (47)*	*p=0.146*

Systolic blood pressure (mmHg)	*116 ± 22*	*117 ± 23*	*116 ± 21*	*p=0.883*
Diastolic blood pressure (mmHg)	*66 ± 12*	*66 ± 12*	*67 ± 12*	*p=0.602*
Heart rate (bpm)	*73 ± 12*	*74 ± 12*	*73 ± 13*	*p=0.436*
e-GFR (ml/min/1.73^2)	*58.1 ± 23.0*	*58.8 ± 23.2*	*57.3 ± 22.9*	*p=0.708*
Hemoglobin (g/dl)	*12.8 ± 1.9*	*12.9 ± 2.0*	*12.8 ± 1.8*	*p=0.928*
Coronary artery disease	*159 (57)*	*78 (55)*	*81 (59)*	*p=0.257*
Atrial fibrillation	*172 (61)*	*83 (58)*	*89 (65)*	*p=0.143*
*Co-morbidity Score**	*6.2 ± 2.4*	*5.9 ± 2.5*	*6.5 ± 2.3*	***p=0.055***
Mild cognitive impairment	*112 (40)*	*56 (39)*	*56 (41)*	*p=0.695*
Depressive symptom	*98 (35)*	*57 (40)*	*41 (30)*	*p=0.082*
Pharmacotherapy				
ACE inhibitors or ARBs	*213(76)*	*110 (77)*	*103 (75)*	*p=0.632*
Beta blockers	*200 (71)*	*104 (73)*	*96 (70)*	*p=0.626*
Spironolactone	*109 (39)*	*55 (38)*	*54 (39)*	*p=0.870*
Loop diuretic	*232 (83)*	*116 (81)*	*116 (85)*	*p=0.627*
Digoxin	*90 (32)*	*44 (31)*	*46 (34)*	*p=0.615*

Legend: BMI, body mass index (n=246); e-GFR, estimated glomerular filtration rate; ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker. Education status (n=275), lipid profile (n=119), time of CHF diagnosis (n=254) and cognitive impairment (n=269 cases). *Charlson Index of Comorbidity Score

5.5.5 Primary Result from WHICH(?) study [22]

In the WHICH trial 102/143 (71%) HBI versus 104/137 (76%) CBI patients experienced the primary outcome of all-cause hospitalization or death in 12-18 months follow-up (adjusted HR 0.97; 95% CI 0.73-1.30; p=0.861): 96 (67.1%) HBI versus 95 (69.3%) CBI patients had an unplanned hospitalization (p=0.887) and 31 (21.7%) versus 38 (27.7%) died (p=0.252). Median duration of each unplanned hospitalization was significantly less in the HBI group (4.0 [IQR 2.0-7.0] vs. 6.0 [IQR

3.5-13] days; p=0.004). Overall, 75% of all hospitalization was attributable to 64 (23%) patients: comprising 43 (67%) CBI patients (adjusted OR 2.55, 95% CI 1.37-4.73; p=0.003). HBI was associated with significantly less days of all-cause hospitalization (-35%; p=0.003) and for cardiovascular causes (-37%; p=0.025) but not for CHF (-24%; p=0.218). Consequently, health care costs ($AU3.93 vs. $AU5.53 million) were significantly less for the HBI group (median $AU34 [IQR 13-81] vs. $AU41 [13-107] per day; p=0.030).

5.5.6 Analysis on the composite outcome

Initial analyses were carried out to compare the multidisciplinary CHF management delivered via an outreach and the HBI with an outpatient, CHF specialised CBI on three above mentioned composite outcomes. To ensure all patients had an equal follow-up duration, patients with follow-up greater than 12 months were censored at the date of contact at 12 months. This was necessary for Patient Journey composite outcome where equivalent follow-up duration was required for all 280 patients. Subsequently, to gain insight into the relationship among composite outcomes that measures similar components, namely mortality, hospitalisation and QoL, information on patients from CBI and HBI were combined.

Estimated Packer's score

All-cause mortality and hospitalisation for worsening HF were examined as an indicative variable during the course of 12 months follow up. If a patient died or was hospitalised due to worsening heart failure, they were placed in "worse" group. Patients were judged to have improved if they had not experienced death or HF hospitalisation and had demonstrated improvement in NYHA functional class or QoL at 12 months follow-up.

The change in NYHA functional class from baseline to 12 months follow-up was assessed. If no final follow-up NYHA functional class was reported, the patient was assumed to be in the same state as at baseline. In this study, the result from heart failure specific QoL instrument, MLWHFQ was used to derive patient global assessment. The MLWHFQ is most widely used heart failure specific instrument with an excellent psychometric properties [23]. This is a self-administered

instrument consisting of 21 questions on patients' perception of the effects of heart failure and its treatment. The questionnaire focuses on the physical, socioeconomic and psychological aspects of QoL, with a response format ranging from 0 to 5 for each question. The total score ranges from 0 to 105, with higher scores indicating a poorer QoL[24]. Using MLWHFQ instead of global patient QoL score for Packer's composite, more specific and sensitive measures of QoL would be included in the Packer's score.

In WHICH(?) trial [8], MLWHFQ was administered at baseline, 6, 12, and 18 months. However for the purpose of this study, a changed score for MLWHFQ was obtained by subtracting 12 month follow up from baseline scores. Any missing value for MLWHFQ was replaced with last observation carried forward. A change of 5 points in the MLWHFQ is considered MID [25]. Subsequently, one class change in patient's global QoL was considered equivalent to 5 point change in MLWHFQ.

In Packer's score, patients who have not been classified as worse or improved were classified as unchanged (Table 5.1).

Estimated Cleland's Patient Journey

To derive Patient Journey, it is essential first to calculate DAOH. For each patient in the study, the total potential follow-up duration was determined as total number of days between baseline to 12 month follow-up. To obtain total days in hospital, the summation of the duration of each individual all-cause hospitalisation were calculated. In a case where the patient died, the number of days from their death to the end of the study was calculated as days lost due to death. Total days in hospital and days lost to death were then subtracted from total potential follow-up days to obtain DAOH. Patient Journey was constructed by applying Australian derived EuroQuol 5D (EQ-5D) indices [26] to DAOH.

The EQ-5D instrument [27] is a widely used generic measure of QoL consisting of five dimensions, mobility, self-care, usual activities, pain/discomfort and anxiety/depression with each having three levels. The EQ-5D has been shown to have satisfactory validity and reliability as an outcome measure in the

cardiovascular area [28, 29].The main advantage of EQ-5D is that it can be used to generate a single index value or utility measure [27]. In addition, in recent times, weights for 243 health states in EQ-5D has been derived for Australian population [26]. For the purpose of derivation of Patient's Journey, instead of using the weights derived from discrete five point patient's QoL scales, Australian derived preference measures of EQ-5D index were used. This eliminates the need to translate how patients feel into a utility measure [26]. It is expected EQ-5D would provide better utility indices than weights applied to patient global QoL [30].

In the trial [8], EQ-5D indices were reported at baseline, 6, 12 and 18 months but indices at baseline, 6 and 12 months were only used to calculate the mean over the 12 months follow-up. This calculated mean for EQ-5D indices were then adjusted for increase in diuretics use before being applied to DAOH.

African American Heart Failure Trial composite outcome

This composite outcome is made up of weighted values for death from any cause, a first heart failure hospitalisation during the 12 months follow-up period and a change in the HF specific QoL at 12 months. Original A-HeFT scores [7] assessed changes in the QoL at six months. However for the purpose of this study, 12 months was chosen as it represents the minimum follow-up period and all components for the selected composite outcomes are assessed at 12 months follow-up (Table 5.1). Methods used to derive all-cause mortality, first heart failure hospitalisation and a change in MLWHFQ is similar to Packer's score. All-cause mortality and first hospitalisation due to worsening HF were examined as an indicator variable (0=no/1=yes) albeit in A-HeFT composite outcome death at any time acquires -3 and a first hospitalization from HF -1. The changes in MLWHFQ scores were assigned from -2 to 2 depending on the degree of improvement or worsening of QoL (Table 5.1). Although the derivation method appears to be similar to the Packer's composite, the major difference is that all patients are assigned a numeric value rather than qualitative outcome as in Packer's score [31].

5.5.7 Statistical analysis

Descriptive analysis in the form of counts (and percentage) for each components of the composite for nominal data and the mean, median and inter quartile range (IQR) for scale measures were found. Using the data from WHICH(?) study [8] the final weights (or percentage) assigned to each component (mortality, hospitalisation and QoL) to the total score were examined for all three composite outcomes to provide an understanding of the magnitude of the influence each components has on the final composite outcome.

Assessment of difference between study assignment

To assess the difference between HBI and CBI, a Mann-Whitney nonparametric test was used for A-HeFT scores and Patient Journey and their components due to non-normality of both composite scores and their components. For Packer's score, chi-square test was used. To compare the difference in study assignment for the Packer's score and unweighted A-HeFT score, all-cause mortality and hospitalisation were analysed using Cox proportional-hazards regression

Association between composite outcomes

The association between the composite outcomes were assessed by Spearman's rho (ρ) and for ordinal measures of association, Goodman Kruskal's Gamma (γ)[32] was used. To further analyse the relationship between A-HeFT and Packer's score a Kruskall-Wallis nonparametric test was used. In addition to assist in assessing association, Patient's Journey as expressed as days lost was found for each category of Packer's score and for A-HeFT scores. All data analyses were performed with Statistical Package for Social Sciences (SPSS) for Windows version 19.0 (SPSS Inc, Chicago, Illinois).

5.6 Result

In 12 months follow-up, a total of 57 (57/280; 20.4%) deaths were recorded. Of these, 46 patients (46/57; 80.7%) had at least one unplanned hospitalisation where 39 (39/57; 68.4%) were for worsening HF. A total of 200 (71.4%) patients had (all cause) hospitalisation with 120 (60.0%) having multiple hospitalisation resulting in a total of 3,715 hospital days. 111 (39.6%) patients were hospitalised due to

worsening heart failure, resulting in 1,568 hospital days (Table 5.3). The mean duration of hospital stay for HF was 14.1 days (sd=15.1, median=9.0, IQR=15.0). Using NYHA functional class, only 8 (2.9%) patients have deteriorated over 12 months follow-up, while 98 (35.0%) patients improved. Most common NYHA functional class over 12 months follow-up was class III (n=189; 67.5%). The mean EQ-5D index was 0.70 (sd=0.19). Changes in QoL from baseline to 12 months follow-up were assessed using MLWHFQ where 51 (18.2%) patients indicated their condition have deteriorated, while 124 (44.3%) have improved in their condition. An increase in diuretics use usually indicates a worsening symptoms or signs of HF [5]. In this cohort, 29 (10.4%) patients required increase in diuretic therapy.

Table 5.3. Component outcome characteristics in 12 months follow-up (n=280)

Component outcome	**n (%)**
All cause death	57 (20.4)
Hospitalisation	
All cause	200 (71.4)
1 hospitalisation	80 (28.6)
> 1 hospitalisation	120 (42.8)
Length of stay – Mean (Median; SD)	18.6 (9.5; 21.4)
Unplanned	175 (62.5)
1 hospitalisation	83 (29.3)
> 1 hospitalisation	92 (33.2)
Length of stay – Mean (Median; SD)	17.8 (10.0; 20.5)
Hospitalisation due worsening HF	111 (39.6)
1 hospitalisation	71 (25.4)
> 1 hospitalisation	40 (14.2)
Length of stay – Mean (Median; SD)	14.1 (9.0; 15.4)
Change in Minnesota Living with Heart Failure score	9.2 (1.0;22.4)

Component outcome	n (%)
(Baseline – Follow-up) - Mean (SD)*	
Improvement by 10 units or more	104 (37.1)
Improvement by 5-9 units	20 (7.1)
Change by <5 units	103 (37.1)
Worsening by 5-9 units	7 (2.5)
Worsening by 10 units or more	44 (15.7)
Change in the New York Heart Association functional class	
Improved by two class	19 (6.8)
Improved by one class	79 (28.2)
Same	174 (62.1)
Worsened by one class	8 (2.9)
Change in diuretic use	
Increase	29 (10.4)
Same	221 (79.0)
Decrease	30 (10.7)

*+ve value indicates improvement

5.6.1 Estimated Packer's composite outcome

The reasons for patients to be placed in worsened, improved, or same category are listed in Table 5.4. Of the 86 (30.7%) patients classified as improved, 44 (44/86; 51.2%) patients improved in both NYHA functional class as well as in patient assessment of QoL, suggesting that there is a moderate agreement between patient assessment of their QoL and NYHA functional class as assessed by clinicians (Table 5.4). More patients were classified as improved from changes in patient assessment than from NYHA functional class (36.0% Vs 12.8%), indicating patient assessment may have been more sensitive in determining patient's QoL. 30 (10.7%) patients were classified as unchanged.

Table 5.4. Packer's composite response details (n=280)

Composite response details	n (%)
Worsened	*164 (58.6)*
Death	18 (11.0)
Hospitalisation due worsening HF	111 (67.7)
Worsened patient assessment or NYHA functional class	35 (21.3)
Unchanged	*30(10.7)*
Improved	*86 (30.7)*
Improved on patient assessment and NYHA functional class	44 (51.2)
Improved NYHA functional class only	11 (12.8)
Improved patient assessment only	31 (36.0)

Of 280 patients, 164 (58.6%) worsened in their composite outcome at 1 year follow-up. The most common reason for being classified in worse category was HF hospitalisation (111/164; 67.7%), followed by worsening in patient QoL assessment or NYHA functional class (35/164; 21.3%). Only 18 (18/164; 11.0%) patients were classified in worse category due to death. Interestingly, amongst those who have been hospitalised during 12 months and hence classified into worse class, 46 (46/111; 41.4%) patients have reported improvement in their QoL/NYHA functional class.

5.6.2 Estimated Patient Journey

Overall, patients lost 40.94% of days of life (41,676 days) from mortality, hospitalisation, QoL measure and a change in diuretic therapy (Table 5.5). The largest proportion of days lost was from limited QoL (24,867 days; 59.7% of the total days lost) followed by mortality (12,354 days; 29.6% of the total days lost).

Other reasons for days lost include all-cause hospitalisation (3,715; 8.9% of the total days lost) and adjustment for increased use in diuretics (740 days; 1.8% of the total days lost). Patient Journey, only assesses deteriorating condition as it is assumed all CHF patients have symptoms that impacts on their lives [5]. In this study, 71 (25.4%) patients were not hospitalised nor died hence only loss of days were due to limited QoL. In fact, even after adjusting with EQ-5D index, 41 (14.6%) patients retained full maximum days.

Table 5.5. Patient Journey and response detail (n=280)

	All (n=280)	
	Total	**%**
Potential days	101,787	
Days lost to		
Death	12,354	12.14
Hospitalisation*	3,715	3.65
Impaired QoL#	24,867	24.43
Diuretic adjustment	740	0.73
Total days lost	41,676	40.94
Patient Journey	60,111	59.06

*All hospitalisation (unplanned and elective) for all causes; #Using Australian based mean EQ-5D indices.

5.6.3 African American Heart Failure Trial composite outcome

The A-HeFT composite score consisted of weighted values for death from any causes, a first adjudicated HF hospitalization, and change in the QoL. In this study 110 (39.5%) had overall A-HeFT positive score, 49 patients (17.5%) with overall score of 0 and 119 (42.8%) with negative score. The mean was -0.5 (sd=2.1; median =0.0; IQR =3.0). 23.7% (n=66) patients achieved a maximum score of 2, a highest possible score for A-HeFT composite. This score can only be achieved in the

absence of death and HF hospitalisation, and a marked improvement in QoL scores (ie. Change of 10 or more points in MLWHFQ). Three (1.1%) patients scored -6, a lowest possible score which can only be achieved with markedly worsening of QoL, first HF hospitalisation and death (Table 5.6).

Table 5.6. Distribution of African American Heart Failure Trial composite score (n=278*)

A-HeFT score	**n (%)**
-6	3 (1.1)
-4	31 (11.2)
-3	31 (11.2)
-2	34 (12.2)
-1	20 (7.2)
0	49 (17.6)
1	44 (15.8)
2	66 (23.7)
Total	278 (100.0)
Mean ±SD	-0.5 ± 2.1
Median ± IQR	0.0 ± 3.0

*2 patients were excluded from the analysis

With A-HeFT composite scores, indication of improvement as expressed in positive overall scores can only be achieved with an increase in QoL scores. However indication of deterioration (negative score) is measured with death, first hospitalisation and worsening in QoL. In examining the impact of each component of the composite for worsening condition (ie. only negative A-HeFT score), 45.4% were due to death, 29.4% to first hospitalisation and 25.2% to worsening of QoL (Table 5.7).

Table 5.7. Derivation of weights assigned to African American Heart Failure Trial composite response (n=278)

Composite scoring system	Criteria	Score	n (%)	Weight assigned to the score (Score X n)	%
Death	Death from any cause anytime during the 12 month followup	-3	57 (20.4)	-171	45.4
Hospitalisation	A first hospitalisation for heart failure	-1	111 (39.6)	-111	29.4
Change in QoL at 12 months	Increased by 10 or more units = markedly worsened	-2	44 (15.7)	-88	25.2
	Increased by 5 to 9 units = worsened	-1	7 (2.5)	-7	
	Changed by -4 to 4 units = no change	0	103 (36.8)	0	
	Reduction by -5 to -9 units = improvement	1	20 (7.1)	20	
	Reduction by -10 or more units = markedly improvement	2	104 (37.1)	208	

Despite all three composite outcomes incorporating mortality, hospitalisation and QoL, the contribution of each individual component to the final outcomes were different. Using the data from WHICH(?) trial [8], the component with the most influence for the Packer's ordinal composite score [6] was hospitalization (67.7%) while in Patient Journey [5] it was QoL (61.5%) and for A-HeFT composite score [33] it was mortality (45.4%) (Table 5.8).

Table 5.8. Percentage contribution of each components to Packer's score, Patient Journey and African American Heart Failure Trial score for deteriorating conditions (n=280)

Components	Percentage (%) contribution to deteriorating condition		
	Packer's score	**Patient Journey**	**A-HeFT**
Death	11.0	29.6	45.4
Hospitalisation	67.7	8.9	29.4
QoL	21.3	61.5	25.2

5.6.4 Application of Composite outcomes to compare Clinical based intervention and Home based intervention

With the significance level set at 0.05, a two way chi-square showed a non-significant association between Packer's score and the study assignment (HBI or CBI) ($\chi 2(2, N=280) = 1.39$, $p=0.50$). The frequencies are shown in Table 5.9.

Similarly, there was no statistical significant difference between the study assignment and A-HeFT score ($p=0.30$) nor between study assignment and Patient Journey ($p=0.21$). Only component of Patient Journey marginally significant between HBI and CBI was days lost due to hospitalisation ($p=0.04$). However considering multiple testings were carried out on Patient Journey and its components, this result is not significant when compared against adjusted alpha level (adjusted alpha=0.008). Descriptive statistics for Patient Journey and its components are reported in Table 5.10. A-HeFT scores and its descriptive statistics of HBI and CBI groups are reported in Table 5.11

To assess the group difference of the component all-cause mortality and hospitalisation for the Packer's score and A-HeFT score hazard ratio were examined. They were all not significant (Table 5.12).

Table 5.9. Frequency of Packer's score by chronic heart failure management group (n=280)

Group	Packer's score			
	Worse	**Same**	**Better**	**Total**
HBI	79 (55.2)	16 (11.2)	48 (33.6)	143
CBI	85 (62.0)	14 (10.2)	38 (27.7)	137
Total	164 (58.6)	30 (10.7)	86 (30.7)	280

Table 5.10. Descriptive statistics of Patient's Journey for study assignment (n=280)

Patient Journey	CHF Management						Mann-Whiney Test
	HBI (n=143)		**CBI (n=137)**		**Total (n=280)**		
	M (SD)	Md (IQR)	M (SD)	Md (IQR)	M (SD)	Md (IQR)	p-value
Potential days	363.7 (7.9)	365.0 (0.0)	363.4 (6.5)	365.0 (0.0)	363.5 (7.2)	365.0 (0.0)	0.3
Days lost to							
Death	39.4 (94.3)	0.0 (0.0)	49.1 (103.8)	0.0 (0.0)	44.1 (99.0)	0.0 (0.0)	0.5
Hospitalisation	9.9 (15.8)	2.0 (14.0)	16.8 (23.1)	6.0 (25.5)	13.3 (20.0)	5.0 (18.0)	0.04
Impaired QoL	91.6 (66.2)	83.6 (79.3)	85.9 (55.9)	84.1 (79.0)	88.8 (61.4)	83.7 (79.8)	0.7
Diuretic adjustment	2.5 (7.7)	0.0 (0.0)	2.8 (7.9)	0.0 (0.0)	2.6 (7.8)	0.0 (0.0)	0.8
Patient Journey	220.2 (95.6)	246.8 (123.5)	208.9 (94.8)	236.7 (130.5)	214.7 (95.2)	239.7 (122.9)	0.2

Table 5.11. Descriptive Statistics of African American Heart Failure Trial score for study assignments (n=280)

Groups	n	M	Mdn	SD	IQR
HBI	143	-0.37	0.0	2.03	3.00
CBI	135	-0.70	0.0	2.24	5.00
Total	278	-0.53	0.0	2.14	3.00

Table 5.12. Clinical events* during one year follow-up (n=280)

Event	HBI[a] (n=143) n(%)	CBI[b] (n=137) n(%)	Hazard Ratio[#] (95% CI)	p-value
All cause death	27 (18.9)	30 (21.9)	0.84 (0.50 – 1.41)	0.51
HF hospitalisation	53 (37.1)	58 (42.3)	0.86 (0.60 – 1.25)	0.44
Death or HF hosp.	62 (43.6)	67 (48.9)	0.87 (0.62 - 1.23)	0.43

*Events are not mutually exclusive; # Hazard ratios are based on Cox proportional-hazards regression models applied to an analysis of the time to the first event.

5.6.5 Relationship between Packer's composite, Patient Journey and African American Heart Failure Trial

The correlation coefficients demonstrate substantial associations amongst all three composite outcomes. The correlation between Packer's score and Patient Journey was moderate (γ =0.49). Examining Patient Journey for each category of Packer composite score demonstrated good agreement between Packer's score and Patient Journey days. Patients in worse category in Packer's score lost 50.9% of all potential days to mortality, hospitalisation and impaired QoL, while in same category, 23.4% of the days were lost and in better, 28.2% (Table 5.13). This

substantial difference in days lost in worse category to the same and better is driven by days lost due to mortality and hospitalisation. In the worse category, 20.7% of days were lost due to death while no days were lost to mortality in the same and better categories. Similarly in the worse category (5.1%) larger proportion of days were lost to hospitalisation than in the same category (1.5%) or in the better category (1.6%). The pattern and magnitude of proportion of days lost was similar between same and better categories of Packer's score (Table 5.13).

Table 5.13. Patient Journey by Packer's score (n=280)

Patient Journey	Packer's score					
	Worse (n=164)		Same (n=30)		Better (n=86)	
	Total	%	Total	%	Total	%
Potential days	59,599		10,950		31,238	
Days lost to						
Death	12,354	20.7%	-	0.00%	0	0.0%
Hospitalisation	3,056	5.1%	166	1.5%	493	1.6%
Impaired QoL	14,497	24.3%	2,347	21.4%	8,023	25.7%
Diuretic adjustment	403	0.7%	53	0.5%	284	0.9%
Total days lost	30,310	50.9%	2,566	23.4%	8,800	28.2%
Patient Journey	29,289	49.1%	8,384	76.6%	22,438	71.8%

A similar pattern emerged between Patient Journey and A-HeFT score. The correlation between Patient Journey and A-HeFT score was moderate ($\rho = 0.54$) (see Figure 5.1). For lower scores of A-HeFT scores (from -6 to -3) more than 50% of days were lost to mortality, hospitalisation and impaired QoL driven mainly by days lost to mortality (Table 5.14). In fact for A-HeFT scores from -6 to -3, the cause of largest proportion of days lost was mortality followed by impaired QoL. However for A-HeFT scores between -2 and 2, the greatest days lost was from impaired QoL followed by death and hospitalisation.

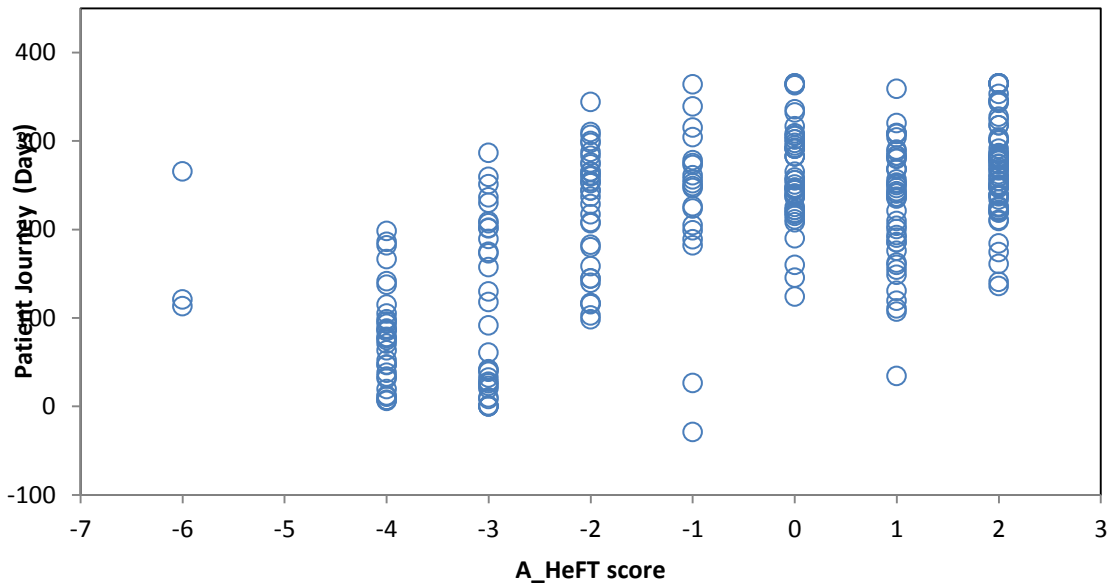

Figure 5.1 Scatterplot of African American Herat Failure Trial with Patient Journey

Table 5.14. Patient Journey by African American Heart Failure Trial composite

	A-HeFT Score								
	-6	**-5**	**-4**	**-3**	**-2**	**-1**	**0**	**1**	**2**
	Days (%)	**Days (%)**	**Days (%)**	**Days (%)**	**Days (%)**	**Days (%)**	**Days (%)**	**Days (%)**	**Days (%)**
Potential days	1,095	-	11,315	11,278	12,308	7,263.00	17,871	15,967	23,960
Days lost to									
Death	269 (24.6)	-	7,003 (61.9)	4,642 (41.2)	392 (3.2)	48 (0.7)	-	-	-
Hospitalisation	81 (7.4)	-	676 (6.0)	732 (6.5)	324 (2.6)	446 (6.1)	338 (1.9)	782 (4.9)	281 (1.2)
Impaired QoL	246 (22.4)	-	1,181 (10.4)	2,387 (21.2)	3,885 (31.6)	2,057 (28.3)	4,424 (24.8)	5,0807 (31.9)	5,438 (22.7)
Diuretic adjustment	-	-	-	70 (0.6)	131 (1.1)	75 (1.0)	106 (0.6)	97 (0.6)	236 (1.0)
Total days lost	596 (54.4)	-	8,860 (78.3)	7,831 (69.4)	4,732 (38.4)	2,627 (36.2)	4,869 (27.2)	5,966 (37.4)	5,956 (24.9)
Patient Journey	499 (45.6)	-	2,455 (21.7)	3,447 (30.6)	7,576 (61.6)	4,636 (63.8)	13,002 (72.8)	10,001 (62.6)	18,004 (75.1)

The overall correlation between Packer's and A-HeFT score was γ =0.86. A Krusal-Wallis nonparametric test was used to analyse the A-HeFT score for the Packer's scores. The result was highly significant (χ2 (2, N=278) = 156.967, p<001). Three post hoc comparisons between pairwise means were conducted using the Mann-Whitney test, and an adjusted alpha of 0.017. All three tests were all statistically significant, where a lowest median score was achieved in worse category, followed by same and then the highest in the better category. Descriptive statistics are shown in Table 5.15 (see Figure 5.2).

Table 5.15. Descriptive statistics on African American Heart Failure Trial score for Packer's composite (n=278)

Packer score	n	M	Mdn	SD	Range
Worse	162	-1.77	-2.00	1.89	8
Same	30	0.00	0.00	0.00	0
Better	86	1.62	2.00	0.71	2
Total	278	-0.53	0.00	2.14	8

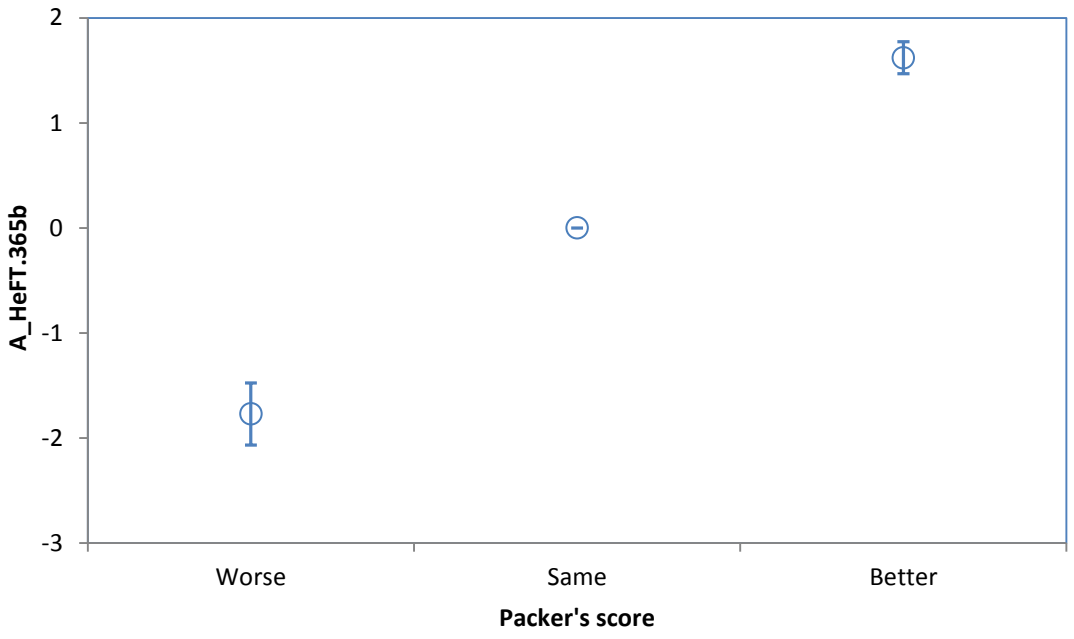

Figure 5.2. Error bar of African American Heart Failure Trial with Packer's score

5.7 Discussion

Quantifying health in terms of death and disease rates in chronic condition is seen to be increasingly inadequate. Developing a core outcome set including QoL oriented PROs alongside mortality and hospitalisation would enable evidence synthesis across different studies. As a consequence of the shortfall of each unidimensional measurement, a composite outcome aggregating multidimensional concepts has emerged to provide a multifaceted profile that cannot be represented by any individual outcome alone. This study compared Packer's score, Patient Journey and A-HeFT score, where three composite outcomes that incorporated mortality, hospitalisation and QoL. It also examined the methodological issues in derivation of each composite outcome to gain insights into the relationship among three composite outcomes. As there is no established gold standard for assessing the absolute effect on any outcome measure, it would be premature to assess which composite outcome is the 'best'. Most likely the 'best' measure would be the one that addresses the research question most appropriately.

Interestingly, all three composite outcomes provided similar result for the comparison between HBI and CBI study. This may be due to synergies in the outcomes mortality, hospitalization and QoL.

5.7.1 Packer's score

The Packer's score is perhaps the most well-known and widely used composite outcome in CHF [34]. Deriving this composite requires two stages. First, it involves 'time to event' methods, where patients are monitored until the death or first HF hospitalisation within the follow-up period. Second, those who are alive at follow-up and have not been hospitalised for HF will be assess for a change in their QoL score and/or NYHA functional class. Depending on the magnitude of the change in QoL/NYHA, patients will be classified into either 'worse', 'same' or 'improved' group. Consequently, this composite outcome provides only a qualitative assessment.

In the first stage of the derivation method, death and HF hospitalisation are considered to have the same weight despite the fact that patients may view these

components of the composite very differently. As HF hospitalisation occurs more frequently than death, the patient's final outcome may be determined more frequently by HF hospitalisation rather than less frequent but more serious outcome, mortality. As demonstrated in this study (Table 5.8) this inordinate weight assigned to HF hospitalisation would have the potential to create a problem in interpreting the result due to the variation in clinical importance [16]. A patient who has a single, short, early admission is placed into 'worse' category similarly to death, when in fact a short HF hospitalisation may reflect early detection of problems and hence a good care rather than an adverse outcome. In this study 41.4% of patients who were hospitalised during 12 month follow-up also reported improvement in their QoL. This implies that hospitalisation for HF does not necessarily indicate worse outcomes.

The information used on the component HF hospitalisation is an indicator variable. Hence, information on duration and severity of the HF hospitalisation are not captured in this composite outcome. Furthermore, this component only considers the first HF hospitalisation, disregarding the subsequent HF hospitalisation despite 36% of patients had multiple hospitalisations due to worsening HF in this study.

In the second stage of categorisation, assessing changes in NYHA functional class and patient assessment during the follow-up period would only be on patients who have not been censored due to death or HF hospitalisation. Consequently, the analysis of QoL component would be per protocol rather than on intention to treat basis. In addition, mortality and hospitalisation is prioritised above QoL component and the changes in QoL component would only come into effect to those who have survived and not been hospitalised. Hence it is not surprising the Packer's score is most influenced by first hospitalisation rather than mortality or QoL components (Table 5.8).

One of the strengths of the Packer's score is that it considers the change in QoL from both the patient and clinician perspective with equal weight. However, this may potentially create a problem when they differ significantly or contradict each

other. Just over 50% of agreement was observed between NYHA functional class and the patient's assessment in this study.

5.7.2 Patient Journey

Patient journey is different to other composites. QoL scores are assessed on an absolute scale rather than as a change from baseline. This has the advantage of avoiding the problem of recall bias of symptoms/QoL and of the variability that may result due to temporary deterioration. However, to increase internal validity of the result, QoL scores at baseline in comparison groups need to be similar. In addition, the duration of the follow-up need to be comparable amongst comparison groups, especially as the final outcome is expressed as total days for each group rather than the mean days.

Patient Journey usually leads to a highly skewed outcome with many patients at a near perfect score. In this study, 71 (25.4%) patients were not hospitalised nor died. Even after adjusting with EQ-5D index, 41 (14.6%) patients achieved the maximum score. Such skewed data are usually difficult to analyse and less powerful nonparametric methods would need to be utilised [11].

In the metric of the Patient's Journey, the DAOH are usually adjusted by arbitrary weights assigned to five point patient QoL score. Given days lost due to QoL has potentially the largest impact on Patient Journey (Table 5.8), these weights can have greatest influence on the final outcome. Yet, these weights have not been validated [35] and in general, there would be disagreement among clinicians and patients about the value and the appropriateness of these weights. In present study, EQ-5D index was used for Patient Journey. This may provide more sensitive and appropriate weight [30]. In addition Patient Journey focuses on the deteriorating state. Any improvement cannot be measured with this composite outcome.

5.7.3 African American Heart Failure Trial composite score

A major strength of an A-HeFT composite outcome is that patients can contribute to all components of the outcome. However in the computation of the score only

first HF hospitalisation is captured. The explanation provided is that this would avoid multiple HF hospitalisations to add up to a score equivalent to death [31]. Hence in this composite outcome, death is considered as the worst outcome and, death at any time from any cause receives the worst score.

One of the interesting feature of the A-HeFT composite outcome is the change in QoL is given a wide range of weights, and it can potentially have bigger influence on the final outcome than hospitalisation. Having a big change in QoL is considered twice as important as first HF hospitalisation. However, when only negative A-HeFT scores (worsening condition) were examined, hospitalisation had marginally larger impact on the final outcome than QoL in this present study. Major disadvantage to A-HeFT score is that the weight assigned to each component have not been validated. Consequently, the magnitude of clinically meaningful difference would be difficult to achieve.

Although there was a moderate correlation between the Packer's score and the Patient Journey, and also between the A-HeFT score and Patient Journey in this analysis, there was no clear pattern when patients have improved or remained the same. In all three composite outcomes the focus was on deteriorating clinical status. Hence their use is limited to measuring worsening clinical status and not of improvement. This is especially the case in Patient Journey which only considers deteriorating state. Interestingly, in Packer's score and A-HeFT composite, only component that would determine patients as improved or same is QoL component albeit they must be alive and have not been hospitalised.

The only pair of scores with high correlations is between the A-HeFT and Packer's score with some pattern emerging. This may be due to using same outcome measures, namely all-cause mortality and first HF hospitalisation as an indicator variable and MLWHFQ assessed in similar way, albeit with different weight and classification.

In planning a study, one of the most important decisions that investigators make is the choice of the outcome. Besides aiming to include outcomes that are important

to patients, providers and health care system, they need to consider the feasibility of measuring them and the efficacy of the intervention. Hence in choosing the composite outcomes, understanding the value system of the composite will enable potential users to choose appropriately. In this study, the hospitalization component was the most influential in determining deteriorating condition in Packer's ordinal composite score[6] while QoL component was for Patient Journey[5] and mortality in A-HeFT [34] . This information will aid in the interpretation of these composite endpoints as well as provide a rationale for the choice of the composite outcomes.

5.7.4 Limitation

The analysis in present study is a secondary data analysis which is an important limitation. Although each of the three composite outcomes Packer's score, Patient Journey and A-HeFT score, use three similar components (mortality, hospitalisation and QoL), there is no validation study to ensure they measure same concepts, nor to compare against a gold standard for assessing the totality of the interventions.

This study is inherently limited by the fact that the patient global assessment was not available to be used in calculation of Packer's score or Patient Journey. Consequently the results of Packer's score and Patient Journey in this study are estimates of these composite outcomes. However, using the MLWHFQ instead of the patient global assessment for Packer's score may have provided a more detailed description of emotional and physical aspects of QoL than the one-item QoL score from patient's global assessment [36]. Similarly in calculation of Patient Journey, EQ-5D was used. Given EQ-5D provide better utility value than restricted range of weights that can be applied to patient QoL score with a five point scale (25), the result may provide better reflection of the patient experience.

The derivation of composite outcomes and the examination was limited to one study [8]. This may limit the generalizability of the findings. However the aim of the study was to obtain a better understanding of issues in composite outcome assessment and not to assess validity of these composite outcomes. In addition, as there is no gold standard for assessing the totality of the intervention or an

independent marker of outcomes, the assessment of validity would be rather controversial.

5.8 Chapter Summary

There is a widespread interest in using the composite outcome as a primary outcome in clinical trials to avoid multiplicity issues and pragmatically for reducing sample size. However, trials with a composite primary outcome can be complex and raise challenging issues in group comparisons and making recommendations for clinical practice. This chapter has examined the structural elements of composite outcomes consisting of patient centred outcomes mortality, hospitalisation and QoL in a well-controlled clinical trial. Although, each of the composite outcome has a varying degree of assigning 'weights' to each component, there was a considerable agreement amongst these composite outcomes when estimating deteriorating condition but not when estimating improvements. Appreciating methodological issues in the derivation and interpretation of composite outcomes is important in advancing the science of outcome measurement. This analysis emphasises the importance of achieving consensus in the weighting and calculation of items in measures of composite outcomes to allow comparison of results across clinical trials.

The following chapter provides a discussion of the findings from the previous chapters, followed by implications for policy, practice and research.

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Chapter 6 Implications for policy, practice and research

6.1 Introduction

Incorporating the perspective of patients in clinical trials has been identified as an international priority [1]. This thesis has sought to address the vexed issue of including the perspective of patients in the metrics of health care policy, clinical practice and research. Although patient centred care is commonly espoused as a core value in contemporary health care systems, shifting from rhetoric to reality is more challenging [2].

Beyond the fundamental approach of moving towards partnerships in care and shifting from paternalism we need robust, reliable and valid measures of health outcomes that are important to the patients [3]. The main objective of this thesis has been to investigate outcome measures in chronic conditions that encapsulate issues important to patients and how these wishes are translated into policy and practice. CHF has been used as an exemplar to provide the framework of a comprehensive evaluation model. These data have relevance and salience to many other chronic conditions.

The framework used in this thesis has sought to include the perspectives of an organisation, providers and consumers. This has been developed with a key consideration of incorporating PROs that are meaningful and relevant to patients, their families, clinicians and policy makers for a given population or service. The aim for this PhD project was to address this issue through conducting a series of studies. Specifically this study sought to:

- Examine patient reported outcomes in clinical management and in clinical research (Chapters 2 and 3).
- Investigate patient important outcomes, their utility, relevance and acceptability amongst patients, clinicians, researchers and administrators (Chapter 4)
- Test composite outcomes model that integrate patient important outcomes in clinical trials research (Chapter 5).

This chapter will summarise the findings of each of the aims and identify implications for the policy, practice and research. Finally the chapter will conclude by addressing both the limitations and the implications of the findings of this thesis.

6.2 Importance of patient perspectives

For a syndrome such as CHF which is chronic, incurable with debilitating and distressing symptoms, it is critical that clinical and therapeutic decisions include the patient's own perspective [3] as well as considering the weight of evidence for a therapeutic approach and the assessment of the clinician. Undoubtedly, traditional outcome measures, such as mortality and hospitalisation, remain important in CHF decision making [4]. However, there has been an increased recognition that PROs provide the important additional information in assessing the overall burden of CHF and effectiveness of interventions [5].

Despite the growing recognition, the uptake of PROs in clinical practice [6] has been slow and there is a limited evidence of policy decision informed by PROs. With the advent of patient centred care defined as "care that is respectful of and responsive to individual patient preferences, needs, and values and ensures that patient values guide all clinical decisions" [7, p3], choosing outcome measures that are meaningful to patients have become critical. Undoubtedly, for many patients, outcomes such as mortality and hospitalisation would play a central role and override any consideration for other outcomes. However there is evidence to suggest that in more severely ill patients with distressing and in times disabling symptoms, an improvement in their QoL or symptom relief are more important [8]. Consequently, examining PROs in conjunction to mortality and hospitalisation [9] need to be considered.

Given the indisputable importance of traditional biomedical outcome measures, particularly mortality and morbidity/hospitalisation in CHF, this thesis has explored the importance of PROs in CHF especially its role in clinical management and in policy decisions. Furthermore, PIO, namely mortality, hospitalisation and PROs were examined for relevance, utility and acceptability in patients, health care

professionals and others making decisions and found they were indeed germane and critical.

The implication of this observation is that the combined results from this core outcomes set (mortality, hospitalisation and PROs such as QoL) will communicate clear and simple information that have the same meaning to all key stakeholders and has the important implication for policy, practice and research. This thesis then proceeded to test the combined result from the core outcomes set into a single composite outcome models already in use in CHF clinical trials. The consequence of using a composite outcome is a "net" result that will further facilitate comparability and interpretability of core outcomes set that are patient centred, but also meaningful at both policy and practice level.

6.3 Patient Reported Outcomes in clinical management and in clinical research

Epidemiological transitions from infectious to chronic conditions and evolving treatment paradigms challenges traditional metrics of morbidity and mortality and underscores the importance of assessing PROs, such as QoL [10].

While the number of clinical trials incorporating PROs either as a primary or secondary outcome has been growing exponentially over the last decades, there is an evidence to suggest these outcomes are underutilised in clinical setting [11]. The reasons may lie in the difference in data collection, analysis and reporting in PROs between clinical trials and clinical management. In clinical trials PROs information is collected by research personnel and patients must agree to provide the information to be on protocol. Furthermore, information gathered is fed back to the providers to monitor the progress and treatment decision. In clinical management however, the barriers at provider and system level could prevent collecting and using PROs to derive full benefits. At provider level, barriers would be a lack of competence amongst clinicians in making sense of the result [12] and scepticism of PROs relevance in patient care [13]. At the system level, there would be barriers such as lack of resources to facilitate collection and dissemination of PROs information as well as the will to incorporate PROs information into clinical workflow. All of these

may be due to lack of methodological and reporting rigour of PROs in clinical trials, resulting in ignorance of PROs meaning and its capability.

To explore these issues further, the methodological and reporting rigor of HRQoL oriented PRO measures in RCTs of pharmacological therapy in CHF were assessed [14]. This study found that despite exponential use of HRQoL in CHF trials over the last decade, the reporting was found to be highly variable. Undoubtedly this may have raised concern among clinicians, regulators and even researchers about the meaning, technical quality, interpretability and decision relevance of the HRQoL oriented PROs [15], leading to slow implementation of PROs in clinical practice. Additional to ensuring PRO measures are valid, reliable, responsive to change, clearly interpretable and relevant to decision makers, there is an urgent need to improve the methodological and reporting quality of HRQoL measure in clinical research. This study has proposed a standardized method for measuring and reporting HRQoL measures in CHF clinical trials to aid in the interpretation and application of findings in clinical practice.

Traditional biomedical outcome measures, particularly mortality and morbidity/hospitalisation remain indisputably important in policy decision. However the importance of PROs has not been considered in the policy arena. Various measures of PROs in CHF that would inform policy decision were explored and summarised, and issues such as measurement and utility in the context of policy decision making were discussed. Using the Innovative Care for Chronic Conditions model [16], a review focusing on developing a metric that incorporates PROs in policy planning, implementation and evaluation were extensively examined. This study concluded that effective policy and planning of health services require understanding of the CHF burden and the treatment effectiveness at an individual level that focuses on PROs [17].

6.4 Beyond PROs to PIOs

In order to influence policy and practice, the chosen outcomes need to be relevant and important to key stakeholders including patients, health care providers and others making decisions about health care. The process of selecting outcome can be

complex as selecting inappropriate outcomes may compromise the utility of the information. By placing the patient at the centre, the outcomes deemed important to patients were investigated for their utility and significance to providers and health care system. Mortality, hospitalisation and PRO were selected as being relevant and important to all key stakeholders. These outcomes were proposed as a core outcomes set which could potentially provide a comprehensive, comparable, meaningful and accurate assessment to patient, providers and health care system.

6.5 Test composite outcomes that combine patient important outcomes in clinical trials research

A number of composite outcome measures have been developed to capture the perspective of the patient, clinician as well as including objective measures of health. Using the data from the WHICH? trial, this study compared the performance of the three composite outcomes already in use in CHF clinical trials. The final results of the comparison between the study assignments were consistent. There are moderate agreements amongst the composite outcomes despite the primary driver of each composite outcome for the worsening condition was different. Despite this, achieving consensus in the weighting and calculation of items in measures of composite outcomes are critical.

6.6 Implications for health policy

At policy level, it is important to balance the societal benefits and expenditure. There is a need to understand the relative benefits of the various treatment options for CHF in terms of economic, clinical and QoL outcomes. Outcome measures that currently inform benefits and burdens of CHF at the policy level are CHF incidence, mortality and economic cost [18]. Economic cost of CHF need to be considered both in terms of direct or total costs. Some examples of direct costs include cost of hospitalisation as well as medication. Subsequently in a core outcomes set, hospitalisation can be used as a surrogate marker of resource use and may be appropriate in cost-effectiveness evaluations.

Undeniably, there is clearer information of CHF survival to influence policy than information on issues related to suffering caused by CHF [19]. There is a need to

supplement traditional clinical outcomes such as mortality and hospitalisation with PROs. However PROs are not routinely collected and analysed at the system level. This means PROs such as HRQoL or patient needs and satisfaction with care have had limited influence at this level.

Increasingly, the importance of this issue in driving health care policy is recognised by groups such as PCORI in the US [20] and PROMs in the UK [21]. As illustrated in this thesis these initiatives to cast the light on PROs is largely dependent on the psychometric properties of instruments as well as the vehicle and the mode in which these are delivered.

There is a growing recognition that insufficient attention has been paid to the selection of the outcomes to measure in clinical trials and clinical audit. Outcomes need to be relevant to patients, clinicians, purchasers and policy-makers if the findings of research are to influence practice and future research.

6.7 Implications for practice

In clinical practice, health care providers aim to increase survival, prevent future morbidity and to improve patients' QoL. Consequently outcome measures are needed to monitor the result of care and to supplement any information to improve patient care. Outcomes such as adverse events, mortality and morbidity and/or CHF rehospitalisation are considered to be important outcome measure in practice setting. In recent times, however there has been a growing awareness of the need to take account of patients' perspective, especially in the view of wide discrepancies between clinicians' and patients' assessment of treatment effectiveness and symptoms [22]. Incorporating patients' perspective in the form of PROs means an essential element of patient centred care [23] is being practiced. Indeed, there has been a call to include PROs in routine clinical practice [3]. Individual PROs data can potentially alert providers to the problems they may not been able to be detect otherwise. These measures also provide a way to monitor treatment benefits/risks leading to better patient care. This is also a potentially useful strategy in increasing individuals' participation in their own treatment and also in health care decision making. Patient adherence is a major impediment to the

effectiveness of therapies. Increased patient satisfaction with a treatment has been shown to be related to adherence [24]. Accordingly, evaluating satisfaction with treatment may assist health care providers in understanding the issues influencing treatment adherence and may help identify aspects of the management plan that require improvement to enhance long term treatment outcome [25].

Increasingly CHF patients are being cared for by multidisciplinary teams in which health care providers from different professions work together [26]. PROs facilitate communication amongst the team by providing a common language amongst professions from different background [11] to coordinate optimal patient care. Provider centred outcome measures should ideally require minimal additional resources and minimal disruption to the delivery of care. Furthermore they should be clinically useful and acceptable to patients [27].

Beyond clinical research, obtaining the perspective of patients is critical in everyday encounters. Ensuring PROs are valid, reliable and easily completed should be an important focus of health care professionals. Technological innovations, such as using tablets, shows some promise as well as instruments such as the Dartmouth COOP/WONGA (World Organization of National Colleges, Academies, and Academic Associations of General Practices/Family Physicians) charts[28] which strive to minimise the challenges of literacy and cognition [29]. It is important that patients, their carers and health care professionals are aware of the value of PROs in improving care. Obtaining consensus on standardised measures across health care settings will ensure generation of normative data and increase the skills and expertise of clinicians for incorporating these data in clinical assessment, planning and treatment allocation [30].

6.8 Implications for research

The selection of an outcome is arguably one of the most important steps in clinical trials. CHF clinical trials have traditionally considered relatively objective clinical outcome measures such as mortality, morbidity/hospitalisation or even biological response to treatment. In recent decades, the number of CHF clinical trials incorporating PROs especially HRQoL assessment as a secondary and sometimes as

primary endpoint have increased exponentially [31] [32, 33]. It is recognition that PROs generally compliment other outcomes in the study [34].

The establishment of the Patient-Reported Outcomes Measurement Information System (PROMIS) and the regulatory bodies such as the FDA in the US requesting PROs data for the drug approval decisions [35] have consolidated the role of PROs as an important endpoint in clinical trials. However, there is a limited scientific rigour in reporting of PROs such as HRQoL in CHF studies as reported in this thesis. In CHF clinical trials however, where clinical outcomes such as mortality or morbidity/rehospitalisation may be the primary outcome, methodological issues in PROs assessment may be inadequately addressed. These issues could be resolved by developing a core outcomes set that include PROs. This may accelerate the science of PROs further in data collection, appropriate timing of assessment, adequate statistical analysis as well as in interpretation of the results [36]. In addition, issues of multiplicity and heterogeneity of PROs tools, which has hampered synthesis and summaries of the effect, would be addressed by specifying the standardized PROs measure for all CHF trials.

Development and application of these core outcome set will also address difficulties arising in systematic reviews as a result of heterogeneity in outcome measurements [37]. Standardization of outcomes is needed to combine data from different studies to allow evidence synthesis and to compare data sets. Inconsistent choice of outcome measures means that many meta-analyses are unable to include data from all the relevant studies. For example, the five most accessed Cochrane reviews in 2009, together with the top cited review in that year, all described inconsistencies in the outcomes reported in eligible trials [20]. A call for the standardization of outcomes and nomenclature is a regular conclusion of systematic reviews [21]. In addition, outcome reporting bias, defined as the bias arising from selecting outcomes for publication based on the results, that affects many randomized trials [38] and 'is an under-recognized problem that affects the conclusions in a substantial proportion of Cochrane reviews' [39] would be addressed with the core outcomes set.

6.9 Study Limitation

It is notable that in developing PIOs, we had not directly asked patients what they considered to be the most relevant outcomes. It seems logical that their involvement would help determine the most appropriate outcomes to measure. However, we did derive data from the reviews of the outcomes in heart failure trajectory. Generating consumer views on findings of this study will be an important first step in moving towards a shared set of outcome measures.

As mentioned in Chapter Five, a development of core outcome sets require more than agreeing on the type and number of discrete outcome measure. There needs to be an agreement on how each of these outcomes (mortality, hospitalisation and QoL oriented PROs) is to be defined, measured and interpreted.

6.10 Conclusion

This thesis has identified that a triad of measurement- mortality, hospitalisation and QoL are likely to be of significant to the perspective of patient, provider and health care system. By utilising the same core outcomes important to all participants of health in clinical policy, practice and research, information would be interpretable by all stakeholders of CHF care and findings in one stakeholder may inform other stakeholders. This would be simplified further by using a composite outcome. However, testing the performance of three composite outcomes has emphasised the importance of achieving consensus in the weighting and the methodology in calculating each component in measures of composite outcomes. Advancing this science will require the combination of (i) expert knowledge of the illness trajectory; (ii) appraisal of evidence based interventions; (iii) the perspective of the individual and also a robust background in measurement and analytics.

6.11 References

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Appendices

Appendix 1 Search strategy for Quality in reporting (Chapter 3)

1	"pharmacological therapy".mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
2	"drug therapy".mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
3	Angiotensin-Converting Enzyme Inhibitors/
4	Angiotensin Receptor Blockers {Including Related Terms}
5	ARB$.ab.
6	beta blocker$.tw.
7	beta blocker$/
8	beta blocker$.ab.
9	ACE inhibitor.ab.
10	Adrenergic beta-Antagonists/
11	Aldosterone Antagonists/
12	Diuretics/
13	diuretic$.ab.
14	Furosemide/
15	frusemide.ab.
16	inotrope.ab.
17	digoxin/
18	pharmacotherapy.mp. or exp Drug Therapy/
19	or/1-18
20	heart failure.tw.
21	ventricular dysfunction, left[mh:noexp] {Including Related Terms}
22	cardiomyopathy.tw.

23	left ventricular ejection fraction.tw.
24	cardiac failure.ti.
25	left ventricular dysfunction.ti.
26	LV dysfunction.ti.
27	left ventricular systolic dysfunction.ti.
28	LV systolic dysfunction.ti.
29	left ventricular diastolic dysfunction.ti.
30	LV diastolic dysfunction.ti.
31	(cardiomyopath* or left ventricular ejection fraction* or LV ejection fraction* or LVEF* or LV EF* or left ventricular EF*).tw.
32	or/20-31
33	limit 32 to (english language and yr="1989 - 2009")
34	clinical.ab. or clinical.ti.
35	trial.ab. or trial.ti.
36	34 and 35
37	clinical trial.pt.
38	36 or 37
39	randomization allocation.ab. or randomization allocation.ti.
40	randomised controlled.ab. or randomised controlled.ti.
41	randomised crossover.ab. or randomised crossover.ti.
42	exp clinical trial/
43	randomized controlled trial.pt.
44	Double-Blind Method/
45	(randomized or randomised).ab.

46	(single-blind or double-blind or triple-blind).ab.
47	Cross-Over Studies/
48	trial.ab.
49	randomly.ab.
50	groups.ab.
51	or/42-50
52	36 or 37 or 39 or 40 or 41 or 43 or 45 or 46
53	"Quality of Life"/
54	(quality adj3 life).tw.
55	quality of life.mp.
56	health-related quality of life.mp.
57	HRQL.mp.
58	H$QL.mp.
59	exp health status/
60	patient-reported outcome$.mp.
61	or/53-60
62	19 and 32 and 52 and 61
63	19 and 32 and 52 and 61
64	limit 63 to (english language and yr="1989 - 2009")
65	19 and 32 and 52 and 61
66	limit 65 to (english language and "review articles" and yr="1989 - 2009")
67	64 not 66
68	limit 67 to (english language and yr="1989 - 2001")
69	67 not 68

Appendix 2 Articles Reviewed for Quality in Reporting (Chapter 3)

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Appendix 3 Search Strategy for Patient Important Outcome (Chapter 4)

1	exp heart failure/
2	chronic heart failure.mp.
3	chronic cardiac failure.mp.
4	"outcome assessment (health care)".mp. or "Outcome Assessment (Health Care)"/
5	outcomes assessment.mp.
6	assessment, outcomes.mp.
7	or/1-3
8	endpoint$ assessment.mp.
9	assessment, endpoint$.mp.
10	4 or 5 or 6 or 8 or 9
11	7 and 10
12	limit 11 to (english language and (comment or editorial or "review"))
13	outcome$ classification.mp.
14	classification, outcome$.mp.
15	endpont$ classification.mp.
16	classification, endpoint$.mp.
17	13 or 14
18	7 and 17
19	Patient Satisfaction/ or "Quality of Life"/ or patient reported outcome$.mp.
20	7 and 19

21	limit 20 to (english language and (comment or editorial or "review"))
22	health care outcome$.mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier]
23	7 and 22

Appendix 4 Ethics Curtin University

Curtin University

Memorandum

To	Professor Patricia Davidson, Centre for Cardiovascular and Chronic Care (Sydney Campus)
From	A/Prof Stephan Millett, Chair, Human Research Ethics Committee
Subject	Protocol Extension Approval **HR 05/2008**
Date	14 September 2011
Copy	Mr Phillip Newton, Centre for Cardiovascular and Chronic Care (Sydney Campus) Ms Sungwon Chang, Centre for Cardiovascular and Chronic Care

Office of Research and Development

Human Research Ethics Committee

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Thank you for keeping us informed of the progress of your research. The Human Research Ethics Committee acknowledges receipt of your Form B report, indicating modifications / changes, for the project *"WHICH HEART FAILURE INTERVENTION IS MOST COST-EFFECTIVE AND CONSUMER FRIENDLY IN REDUCING HOSPITAL CARE: THE WHICH? STUDY"*. Your application has been ***approved.***

The Committee notes the following amendments have been approved:

1. We would like to add Ms Sungwon Chang to the list of Curtin investigators for this trial. Sungwon is currently enrolled in her PhD at Curtin and has received her candidacy pending HREC approval. Sungwon will undertake some analyses as part of Phase II of this trial and this will form part of her PhD.

Approval for this project remains until **14-05-2012.**

Your approval number remains **HR 05/2008,** please quote this number in any further correspondence regarding this project.

Please note: An application for renewal may be made with a Form B three years running, after which a new application form (Form A), providing comprehensive details, must be submitted.

Yours sincerely,

Associate Professor Stephan Millett
Chair Human Research Ethics Committee

Appendix 5 Articles published associated with this thesis

Heart Fail Rev
DOI 10.1007/s10741-012-9369-0

Are all outcomes in chronic heart failure rated equally? An argument for a patient-centred approach to outcome assessment

Sungwon Chang · Phillip J. Newton · Sally Inglis · Tim Luckett · Henry Krum · Peter Macdonald · Patricia M. Davidson

Abstract Chronic heart failure (CHF) is a multi-dimensional and complex syndrome. Outcome measures are important for determining both the efficacy and quality of care and capturing the patient's perspective in evaluating the outcomes of health care delivery. Capturing the patient's perspective via patient-reported outcomes is increasingly important; however, including objective measures such as mortality would provide more complete account of outcomes important to patients. Currently, no single measure for CHF outcomes captures all dimensions of the quality of care from the patient's perspective. To describe the role of outcome measures in CHF from the perspective of patients, a structured literature review was undertaken. This review discusses the concepts and methodological issues related to measurement of CHF outcomes. Outcome assessment at the level of the patient, provider and health care system were identified as being important. The perspectives of all stakeholders should be considered when developing an outcomes measurement suite to inform CHF health care. This paper recommends that choice of outcome measures should depend on their ability to provide a comprehensive, comparable, meaningful and accurate assessment that are important to patient.

Keywords Outcome assessment · Patient-centred · Chronic heart failure · Patient important outcome · Outcome measurement · Composite endpoints

Introduction

Chronic heart failure (CHF) is a common, complex syndrome occurring most commonly in the elderly [1]. Recent

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innovation, driven largely by pharmaceutical agents, devices and disease management programs, has led to improved survival [2]. But longevity often comes with an increased burden of disease [3]. Living with CHF is often associated with limited physical, psychosocial and economic capacity [4, 5]. Symptom burden and lengthy, costly re-hospitalisations are defining characteristics of the CHF trajectory [6]. People with CHF often have multiple medical conditions and live with debilitating symptoms such as fatigue and breathlessness. Therefore, the primary objective in the management of CHF is to optimise patient well-being in the context of longer-term survival. Balancing these two perspectives is challenging and requires an understanding of the individual's values and wishes, juxtaposed with those of health professionals and society at large.

Outcome measurement makes an important contribution to describing, interpreting and predicting the effects of disease and the influence of health care interventions. Outcome assessment can be used not only to evaluate the efficacy of interventions but also to describe the impact of care on patients (e.g. patient satisfaction), to support evidence-based clinical decision-making at the individual patient level, and to identify aspects of care for further improvement [7]. Consequently, the concept of outcomes naturally directs attention to the needs of patients and their well-being [8]. The selection of outcome measures should be undertaken and aligned to those important to the patients.

Choosing inappropriate outcome measures may lead to unimportant or misleading information, wasted resources and a loss of opportunity to demonstrate potential benefits. Despite debate on perspectives of management in CHF [9–12], choosing which outcomes to measure from the large range available remains challenging, and researchers and clinicians alike require further guidance [13]. At the same time, there are calls from agencies such as the Food and Drug Administration in the United States for researchers to generate endpoint models that clearly explain the roles and relationships between outcomes in providing an evidence base [14]. As individuals live longer with chronic conditions, the burden from comorbidities increases and assessing the relative contributions of different conditions and treatments becomes increasingly complex [15].

With a growing interest in patient-centred care, seeking to measure outcomes that are important to patients is a natural consequence [14]. Outcomes that are important to patients are those that patients notices, cares about and for which they would be willing to undergo a treatment with associated risk, cost or inconvenience for it to be the only thing that changed [16]. Process measures are those that assess characteristics of care that would influence ultimate outcomes (e.g. medication adherence). Surrogate outcomes are those that are known to predict important outcomes but are easier and quicker to measure (e.g. exercise capacity in CHF). Clinicians and health service managers, planners and policy makers often need intermediate and surrogate measures to monitor progress, understand causal relationships and evaluate cost-effectiveness. But it is important to emphasise that these outcomes should be supportive of, rather than alternative to outcomes that are important to patients.

The purpose of this paper is to review patient important outcome measures used in CHF and discuss methodological issues. The advantages and disadvantages of approaches to outcome measures are included and recommendations for a comprehensive, patient-centred outcome assessment suggested.

Methods

Information sources and search

Electronic databases Medline, Cumulative Index to Nursing & Allied Health Literature (CINAHL) and EMBASE were searched in addition to the World Wide Web using the Google Search Engine. Medical Subject Heading (MeSH) terms and keywords used in this search related to CHF and outcome assessment, outcome classification, health care outcomes and patient outcomes. Searches were not limited to any date range to enable insights into changes that may have occurred in outcome concepts or methods. Further additional data sources, such as clinical guidelines and policies, were hand searched for information relevant to the review. The search was limited to reviews, editorials or comments on outcomes in CHF published in English. Methodological issues pertaining to adverse events [17] and burden of disease (e.g. frequency of tests, clinician assessment of disease burden) [18] were also identified.

Data extraction and synthesis

Data were summarised and managed using Endnote XV (Thomson Reuters, New York) software. Articles retrieved were analysed to identify issues in methodological assessment and relevance to patients. In addition, those outcomes deemed to be important to patients were analysed for their relevance to clinicians and health care systems.

Eligibility criteria

Articles were eligible if they considered concepts and methodological issues related to measurement of outcomes in CHF.

The following questions drove the selection of articles and information.

- What are the measures of health outcomes in CHF?

- What are the outcome measures that have been identified as important to patients in clinical trials and outcome assessment?

Results

The following numbers of references were retrieved for this review: CHF and outcome assessment ($n = 107$), outcome classification ($n = 2$), health care outcomes ($n = 4$) and patient outcomes ($n = 65$) (see supplementary material).

Which measures of health outcomes in CHF are important to patients?

Outcome measures assessed at the individual level in CHF have included survival (mortality) [10], event-free survival, hospitalisation [10], PROs (e.g. symptoms, QOL) [10] and economic outcomes (e.g. cost and resource use per patient) [18]. Outcome measures such as mortality, morbidity as well as PROs such as symptom burden, functional status, psychological state, compliance with a therapeutic regimen, self-management and quality of life are also identified by the American College of Cardiology/American Heart Association (ACC/AHA) as important data elements for assessing the clinical management and outcome of patients with CHF [19].

Mortality

Mortality is a critical outcome measure in CHF especially when it is unexpected, premature or avoidable. Unexpected death may be a result of both cardiac and non-cardiac cause. To be a reliable and valid outcome at the system level, appropriate casemix and severity adjustments need to be made to adjust for these differences [20].

In CHF clinical trials, all-cause mortality has been found favour to be an unbiased and unambiguous endpoint [10] and has been used as a sole primary outcome [9]. However, as CHF care improves, mortality is becoming a less frequent event in some clinical trials, with the result that large sample sizes are required to detect differences between intervention and control groups [10]. This has led in mortality being included as part of a composite endpoint (usually with hospitalisation). This is controversial because of the potential for unequal weighting of events [21].

The choice of all-cause versus cause-specific mortality is also contested [22]. Although all-cause mortality will result in a higher event rate, the inclusion of deaths not the result of cardiovascular disease will invariably reduce sensitivity and therefore power to detect an intervention effect [22]. Assessment of cause-specific mortality improves precision but presupposes no impact on non-cause-specific mortality, which may not necessarily be true.

As well as providing a clearer indication of the effects of management, cause-specific mortality can also provide insights into a broader concept of chronic condition and its mechanism. However, a focus on cause-specific mortality requires researchers to distinguish between cardiovascular death and death caused by comorbidity. The difficulty of adjudicating the cause of death may depend on the quality of documentation provided on the death certificate, particularly for community-based deaths [22]. Furthermore, although cause-specific mortality may provide clinicians and health service operatives with important information to improve care and service delivery, it may not be meaningful to patients or their families for whom the impacts will be the same regardless of cause [22].

Hospitalisation

Data on hospitalisation (e.g. cause of admission, length of stay) provide useful information on prognosis, allow inference regarding the burden of CHF and management on patients and their families, and inform cost-effectiveness analysis [21]. But, despite its utility, hospitalisation as an outcome measure has limitations. Admission to the hospital is influenced by patient and social preference and differences in practice patterns, with thresholds determining admission and length of stay varying according to country, region and even institution [9]. The use of "observational stays" in some institutions and "short stay" [9] holding units in emergency departments further confounds comparison between studies. As with mortality, there is also the dilemma of whether to choose all-cause or cause-specific hospitalisation, with advantages and disadvantages to each [22]. When adjudicating the reason for hospitalisation, the definition of CHF hospitalisation is likely to vary depending on severity of CHF, comorbidities and related admission policies [12].

Patient-reported outcomes (PROs)

Over the past two decades, there has been a growing interest in collecting outcomes that are important to patients to ensure clinical care is person-centred [23]. Implicit in this process is obtaining the perspective of the patient through the use of patient-reported outcome (PRO). PRO is an umbrella term used to capture any outcome relying on patients' perception, interpretation or evaluation of their condition and care [24]. This may include multidimensional constructs such as patient preferences, symptoms, functional status, psychological well-being, quality of life (QOL) and satisfaction with care. Importantly, PROs provide patients with a voice to identify impacts of disease

and care that are important to them [25]. PROs include "any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else" [26]. In CHF, the majority of PROs identified were health-related quality of life (HRQoL) and depression [27].

In clinical practice, PROs can be used to inform health decisions in a wide range of applications from individual patient decision-making through to developing health policy aimed at improving population health [28]. Routine administration of questionnaires to measure PROs can be used to screen for unmet needs [8] or problems such as depression and anxiety [29]. Evaluating satisfaction with treatment may assist providers in understanding the issues influencing treatment adherence and may help identify aspects of management linked to long-term treatment outcomes [30]. PROs can also facilitate communication amongst the health care team by providing a common language amongst professions from different clinical backgrounds [31]. Finally, established discrepancies between clinician and patient perceptions of symptoms and treatment effectiveness mandate collection of patient-reported data to inform future practice [31]. Adding an additional dimension of patient preference and prioritisation of outcomes may be a useful conceptual advance to PROs.

In clinical trials, PROs provide a number of advantages over and above traditional outcomes such as mortality. They offer a way to differentiate benefits when two or more treatments present with similar clinical efficacy [32]; they measure the benefit of "add-on" therapy that has the primary objective of providing an incremental benefit to QOL rather than substantial impact on survival [33]; and they can be used to examine long-term impacts of treatment on daily life in the context of lengthy survival, increasingly an issue in CHF [34]. Adding the additional aspect of a prioritised outcome can potentially lead to informed quality decision-making.

PROs usually reflect unobserved (latent) concept which may manifest themselves in different observable ways depending on the condition or treatment of interest. There is a challenge in selecting the most appropriate measure that would fulfil the objectives of the outcome assessment. It must also be guided by the severity and nature of CHF and ensure PROs measure selected would measure benefits/side effects of the therapy as well as the change in patients as CHF progress [35]. PROs are inherently subjective and rely on patient's self-report [36]. This means it is also imperative for PROs measure to be reliable and valid as well as responsive and relevant [37]. In addition, relying on self-report means PROs data are more prone to missing data than other clinical outcomes [38]. This is an important issue especially in many CHF studies where elderly patients may often drop out of the study due to severe illness or even death. Consequently missing data may lead to bias which may result in an erroneous conclusion [38].

In evaluating PROs, the timing of the outcome assessment is crucial. In most situations, the timing of the assessment of PROs will depend on disease progression, the therapy response, the risk of premature death or adverse events and the respondent burden [37]. Incorrect timing of PROs assessments could potentially jeopardise the reliability and the validity of the PROs findings [39] by biasing the treatment effect. If an evaluation of PROs measure took place outside an accepted time window, the result may be different. In addition, choosing appropriate timing of PROs assessments requires careful consideration of the transient effect of therapy on PROs measure.

PROs data especially quality of life comprise multiple components such as individual's perceived physical, psychological and social well-being [40]. Statistical analyses of these data often result in false significant results due to multiple tests. Several methods have been suggested to address the multiplicity issues such as comparing only the summary score, adjusting p values or to analyse only selected domains [38, 40].

In interpreting PROs, there is a need to determine the minimal important difference (MID). This measure enables interpretation of outcome assessment beyond statistical significance. However, it can be argued a meaningful change is a subjective concept may differ depending on different perspective. There is clearly a need for a comprehensive interpretation strategy that incorporates different anchors, each having its own metric that is meaningful to a given audience [41]. Works have been carried out to establish MID for Minnesota Living With Heart Failure Questionnaire [25] and the Kansas City Cardiomyopathy Questionnaire [42], two most popular HRQoL measures used in CHF.

Adverse events

An adverse event is defined as an unintended harm due to medical management or lack thereof in contrast to complication arising from the underlying disease [17]. Although adverse events may be linked with quality of care and patient safety, presence does not necessarily indicate poor quality, nor their absence indicate good quality [17]. Most patients with CHF have one or more comorbid condition that will potentially cause treatment conflict, [43] especially when multiple medicines are prescribed. This places patients with CHF at risk of adverse outcomes which may be captured by mortality, hospitalisation and PROs (e.g. side effects and symptoms).

Burden of disease

Burden refers to the demands experienced by patients, caregivers, clinicians, the health care system and society [44]. Patients' and carers' burden can be expressed as

mortality, hospitalisation and PROs such as symptom burden [45]. In some instances, economic burden is also described at an individual level. This may include lost productivity as well as direct and indirect costs of care such as hospital transportation [46]. Patients' and carers' burdens are usually linked with expectations of and satisfaction with care [44] as measured via PROs. The burden of CHF at a system level has generally been measured with traditional indices such as incidence, mortality and morbidity and increasingly health services utilisation, particularly hospitalisations [47]. One definition of the burden of disease is a measure of the years of healthy life that an individual or population loses as the result of disease. Generic outcomes that combine both mortality and morbidity into a single index such as disability-adjusted life years have also been used [48]. Identifying the outcomes important to patients such as quality of life is an important consideration in determining disease burden.

Several reviews exploring different endpoint/outcomes in CHF and cardiovascular clinical trials have demonstrated the lack of consensus on appropriate measures [9, 10, 21]. In some CHF clinical trials, there is a recognition that treatment efficacy needs to be measured by multiple outcomes, especially where management or the outcomes of interventions have multiple components [49]. Composite endpoints are useful both for capturing multiple components and additive effects of interventions and also for reducing sample size due to increased event capture.

Composite endpoints

Implicit in applying a composite endpoint is the premise that each of the component endpoint would measure the same underlying pathophysiological process, but be different enough that they add a dimension to the measurement of the disease process that has not been contributed by any other component endpoint [50]. Composite endpoints may include more than one clinical outcome (e.g. major acute coronary event), surrogate outcomes and/or PROs, or a combination of all three [51]. In CHF trials, most commonly used composite primary endpoint is mortality and hospitalisation with or without worsening HF. By combining multiple endpoints with low event rates such as incidence of mortality and morbidity into a single composite endpoint increases the event rate and in turn reducing the sample size to achieve required power [52]. As a result, the trials will become smaller, less costly and the result will be available earlier [52]. However, some argue this comes at a cost of precision and sensitivity [53].

Examples of composite endpoints in CHF trials include Packer's ordinal composite score (improved, unchanged or worse) [54], Cleland's 'patient journey' [55], Braunwald's "weighted unsatisfactory outcome" [56], composite endpoint used in the African American Heart Failure Trial (A-HeFT) [57] and global ranking endpoint [58]. All of these endpoints make an important point in conceptualising the complexity of a multidimensional approach to management and importance of each component to the patient. For example, in Packer's score, patients are classified as "better, the same, or worse'' depending on the patient's vital status and their symptoms. Patients who died or were hospitalised due to worsening heart failure or experienced worsening HF were classified as worse. Patients with improved symptoms and no worsening were classified as better. Patients classified as neither better nor worse were classified as unchanged. Packer's composite endpoint effectively weighs death, hospitalisation and symptoms equally. Another weighting scheme is based on hierarchical endpoints based on ranking of events or global rank approach. In this type of scheme, all patients are ranked on the basis of pre-specified hierarchy of events. For example death would be ranked worst, then hospitalisation and so forth. An alternative to above weighting of schemes is a score calculated for A-HeFT trial. In this scoring system, death is counted as −3, a first hospitalisation from HF is counted as −1 and change in quality of life varies from −2 to 2 depending on the degree of worsening or improvement. This weighting scheme assigns a numeric value to all patients and each patient's experience contributes directly to the total score. A challenge with this weighting scheme is establishing consensus amongst patients, clinicians and regulators on what constitutes a MID. In addition, the relative importance assigned to each component may not achieve agreement amongst all stakeholders. This would create a problem in interpretation when the components are not moving in the same direction.

Outcome assessment in clinical management

In clinical management, the purposes of outcome measurement typically include monitoring and support of patient progress, diagnosis, treatment and communication [59]. Outcomes assessment in clinical management can be targeted at either or both of two levels: at an individual patient care level and/or at an aggregated system level [60]. Information at the system level can be collected and analysed at either the clinic or group practice level.

In clinical management, outcome assessments typically use routine data to avoid undue burden on patients that may not have immediate consequences for their own personal care. Routine outcomes data are subject to numerous biases and are unlikely to be of sufficient quality for rigorous evaluation of treatment efficacy [61]. Nonetheless, outcome data can be utilised in measuring the quality of care, designing system interventions, reallocating resources and research efforts, training health care personnel and characterising a patient population to better understand their needs.

Discussion

The current review has found a range of commentaries and reviews concerning outcomes measures important to patients in CHF yet no gold standard exists. While there was a general agreement that outcomes assessment is essential in improving care, a number of strengths and limitations were highlighted in each of outcome measures important to patients.

Outcomes in CHF are used to describe the impact of treatment/care on patients' lives. Incorporating patients' perspective in the form of PROs means an essential element [62] of patient-centred care is being practiced. Indeed, there has been a call to include PROs in routine clinical practice [33]. Therefore, choosing outcome measures that are meaningful to patients is essential. Traditionally, patient outcomes in CHF have been mortality, hospitalisation and avoiding or decreasing adverse events of care [11]. With debilitating symptoms including fatigue and breathlessness, improving functional status and health-related quality of life (HRQoL) has become patient important outcomes. Patients with CHF often experience multiple medical conditions with unpredictable prognosis with limited physical, psychosocial and economic capacity [4, 5]. Increasingly, patients' perspective as expressed in PROs such as HRQoL, functionality, symptoms (and symptom management) and more recently quality of death have become patient focused outcomes [63].

Increasingly, there is a recognition that patients' desired outcomes may change as the patients and their careers evolve as the disease progresses and treatment/care becomes familiar [64]. Undoubtedly, for many patients, outcomes such as mortality and morbidity/hospitalisation would play a central role and override any consideration for other outcomes. This would be the case, especially in patients with mild symptoms where their prime objective would be to improve survival [65]. However, in more severely ill patients with distressing and in times disabling symptoms, this may not be so; an improvement in their quality of life or symptom relief may be more important [66]. Consequently, in examining patient level outcomes, PROs need to be considered in conjunction to clinical outcomes such as mortality and rehospitalisation [67]. In order to consider the justification for this, it is useful to consider patient, clinician and system perspectives in CHF outcome assessment and these are summarised in Table 1.

Clinician level

In providing care to patients with CHF, clinicians aim to increase survival and improve QOL both by managing current problems and preventing future morbidity. To achieve this, clinicians need to monitor the processes and results of care to inform future improvements to care and support shared decision-making with patients [68]. Process measures include patient understanding of self-management advice, availability of support and adherence to treatment as well as vital signs, laboratory and diagnostic test results and response to medications [13]. Physiological and elemental outcomes such as changes in pulmonary capillary wedge pressure and natriuretic peptide levels may be disease rather than patient-centred but are nonetheless an important part of CHF patient management. They inform clinicians of the status of disease process as well as the mechanism related to the patient problem and a better understanding of the way a treatment works [69]. Process measures should ideally require minimal additional resources and minimal disruption to the delivery of care. Furthermore, they should be clinically useful and acceptable to patients [60]. As much as possible, they should inform concrete action (e.g. provision of information) [67] to improve patient care.

System level

At a system level, outcomes evaluate changes in health of a defined population as a result of health care or health system activity. Outcome measures at this level assist in establishing and evaluating health policies that may benefit CHF communities [27]. Such methods of assessment are critical in informing policy decisions. As demands on resources increase, outcome measures are increasingly needed to enable disparities in burden to be highlighted across different health conditions and geographical regions as well as over time. Outcome measures have an important part to play in examining accessibility of quality CHF care across the population. These applications are needed to ensure the health care system is suitably responsive to the needs of different groups.

Given the escalating health care cost associated with CHF and other chronic conditions, it is important to balance societal benefits with expenditure to allocate care and resources judiciously. There is a need to understand the relative benefits of the various treatment options for CHF in terms of clinical and economic outcomes. The quality adjusted life year (QALY) is widely used for economic evaluation across health care [70]. QALYs combine information on both quantity and quality of life and offer a standard unit for comparison across different interventions and places on the disease trajectory [71]. That said, there have been numerous criticisms of QALYs, especially concerning the methods used to generate their utility weights and the use of QALYs for informing allocation of health care funds between disparate conditions [72]. A broader assessment at system level would include cost-benefit analyses [73] and loss of productivity as possible societal outcomes.

Table 1 Patient, clinician and system perspectives in chronic heart failure outcome assessment

	Perspective		
	Patient	Clinician	System
Reason for interest in outcomes	Minimise risk of CHF	Assess patient needs	Plan services
	Restore to "health" in timely way	Provide appropriate care/treatment	Monitor the quality of care/ treatment provided
	Ability to live a normal life	Monitor quality of care/treatment provided	Justify cost of care
			Improve population health
			Reduce health disparities
Desired outcomes	Timely access to quality care	Patient adherence/ satisfaction	Reduce incidence/prevalence of CHF
	Minimise symptom burden and 'functional limitation	Improved self-management of CHF	Appropriate service provision
	Survival		Improved knowledge and understanding of CHF and related risks.
	Avoid major clinical events such as hospitalisation	Appropriateness of treatment/care provided	Population-based surveillance system
	Self-management of CHF	Avoid adverse events	
	Feel safe and secure and satisfied with care	Good liaison with other health care team	
Possible outcome measures	Mortality	Mortality	Mortality
	QOL	Symptoms (e.g. dyspnoea)	Incidence/prevalence
	(Re)hospitalisation	LVEF	Hospital days
	Functional status	Patient satisfaction	Cost of treatments
	Patient satisfaction		Workforce implications

CHF chronic heart failure, *QOL* quality of life, *LVEF* left ventricular ejection fraction

Two-thirds of the economic burden of CHF can be accounted for by admissions to hospital alone [74], making interventions that avoid (re)admission a priority from the system perspective. At the same time, there is a need to measure hospitalisation and other system outcomes in terms of their impact on the patient [75]. While we may assume that patients generally wish to avoid hospitalisation, it may be that this is a preferred outcome for some people who lack support in the community [76]. PROs such as psychological well-being, unmet needs and satisfaction with care have so far had a limited influence at the systems level. Future work is needed to integrate these measurements into the systems level model.

Moving towards a prioritised, integrative model of outcomes assessment

This review has considered outcome measures of importance to patients and considered their importance at clinician and health care systems level. Mortality, hospitalisation and PROs are outcomes that are relevant and important to all stakeholders of CHF care and have wide application in research and clinical practice. If standardised, this "core set" of outcomes has potential to enable both evaluation of health care effectiveness and monitoring of population health [77]. Identifying consensus in outcomes between patients, providers and health systems is important in generating an integrative model of health care assessment that has utility and relevance. Furthermore, as evaluation metric is often a driver of service organisation and delivery, having a genuinely person-centred outcome goal is likely to alter service provision.

The critical issue is whether this should be approached by developing a single measure, by measuring a core set of outcomes and trying to combine the results as a composite outcome, or by keeping them as a set of individual outcomes. To varying degrees, any single outcome may be inadequate to capture important differences [71]. However, comparability and interpretability of outcome assessment will be greatly facilitated by a simple measure of outcome [78] such as a composite outcome. Combining multiple outcomes into a single summary measure is a useful approach for defining 'net benefit' [79].

In using a composite outcome, we would also circumvent the need to make an allocation for multiple hypotheses testing, as one is essentially dealing with a single endpoint [51]. In addition, the problem of competing risks can be avoided especially if a clinical outcome such as mortality is combined with morbidity (in the form of hospitalisation) [52] and PROs. With the core set of outcomes forming a composite will ensure each component of this outcome is relevant and includes an outcome considered to be important

to the patient. Ensuring reliability, validity and acceptability is critical, and ideally, this composite outcome would lead to greater efficiency and higher quality of care.

To ensure the utility of the composite outcome at all levels of care, each component (from the core set of outcomes) should be appropriately weighted, depending on the purpose and the goal of outcome assessment. Currently, in most studies with composite endpoints, the components are assigned equal weights even though stakeholders, particularly patients, may not consider them equally important. Weighting needs to be undertaken carefully because, if the balance is inappropriate, reduced power may arise [11]. In addition, the problem associated with the interpretation of the treatment effect occurs when the components are moving in different directions, especially when a less frequent endpoint, such as mortality, with much more frequent endpoints such as symptom improvement [52] are combined. Standardising the weights of composite endpoints will allow the patients, providers and health care system to agree on defining a clinically meaningful effect on composite scores [44].

Conclusion

Although the literature challenges conceptual and methodological assumptions of conventional endpoint assessment methods, to date there has been limited application on non-traditional measures [21]. Choosing measures must depend on the capacity to provide comprehensive, comparable, meaningful and accurate reflection of outcomes as well as the capacity for data collection. Measurement issues require issues of reliability, validity and utility in meeting the needs of a range of stakeholders. Importantly, ensuring these metrics needs to meet the priorities of patients. While it is likely that utility will vary from the perspective of patient, clinician and health care system, the needs of clinicians and the system should be seen as supportive of rather than alternative to those important to patients, a core set of outcomes with broad-scale application and appeal. A composite endpoint combining these outcomes offers promise if it is reliable, valid and acceptable to patients, providers and policy makers.

Conflict of Interest Ms S. Chang, Drs P. Newton, S. Inglis, T. Luckett., Profs H. Krum, P. Macdonald and P. Davidson have no conflict of interest or financial ties to disclose.

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Review

What is the methodological and reporting quality of health related quality of life in chronic heart failure clinical trials?

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ABSTRACT

Background: Although the number of clinical trials assessing health related quality of life (HRQoL) in chronic heart failure (CHF) has increased exponentially over the last decade, little is known about the quality of reporting. The purpose of this review was to assess the methodological and reporting rigor of HRQoL in RCTs of pharmacological therapy in CHF.

Methods: The electronic data bases, Medline and EMBASE were searched from 1990 to 2009 using the key search terms 'heart failure' combined with 'quality of life', 'pharmacological therapy' and 'randomized controlled trials'. A total of 136 articles were identified and evaluated according to the "Minimum Standard Checklist (MSC) for Evaluating HRQoL Outcomes".

Results: According to the MSC criteria, 26 (19.1%) studies were considered 'very limited', 91 (66.9%) were 'limited' and only 19 (14.0%) studies were considered to be of a 'probably robust' in terms of methodological and reporting rigor. In fact, the quality of HRQoL reporting has not improved over time.

Conclusion: HRQoL is a critical consideration in CHF management, yet reporting is highly variable. There is a need to develop a standardized method for measuring and reporting HRQoL measures in clinical trials to aid in the interpretation and application of findings.

1. Introduction

Chronic heart failure (CHF) is a common, costly and resource intensive syndrome with a poor prognosis. Patients with CHF experience poor outcomes including severely impaired health related quality of life (HRQoL) [1]. Some studies have shown that patients with CHF experienced a poorer quality of life compared to individuals with other chronic conditions [2,3]. Many patients with advanced CHF also ascribe greater importance to the quality rather than the length of their life [4].

The number of clinical trials incorporating HRQoL assessment as an endpoint has increased in recent decades [5]. Increasingly CHF clinical trials focus on the benefit of "add-on" therapy for which the cumulative benefits may be an incremental gain in HRQoL, in spite of a limited impact on survival [6]. This increased focus on incremental benefit means that methods of assessment and reporting of endpoints such as HRQoL need to be rigorous and robust.

Although the purpose of measuring HRQoL in randomized control trials (RCTs) may have been to guide future patient care and treatment decisions, there is evidence of the limited influence of this approach on individual clinical decision making and/or treatment policies [7]. This may be attributed to inadequate reporting, low compliance with completing study measures, underpowered studies and variable quality in studies assessing HRQoL [8–10]. Furthermore, most clinical trials using HRQoL as an endpoint solely report psychometric properties and do not extend to the issue of relevance of the measure nor to the rigor in measuring and reporting [11]. In spite of mushrooming of HRQoL assessment and as a consequence numerous reviews and meta-analyses on HRQoL in patients with CHF [5,12–14] the methodological and reporting rigor of the HRQoL assessment in RCTs has not been described.

The purpose of this review was to assess the methodological and reporting of HRQoL in RCTs of pharmacological therapy in CHF, either as a primary or secondary endpoint using the "Minimum Standard Checklist (MSC) for Evaluating HRQoL Outcomes" [9] (Table 1). RCTs of pharmacological therapy were chosen for a number of reasons; for its potential for incremental therapeutic benefit [15]; of additive therapies [16]; and the fact that regulatory bodies such as

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Table 1
Level of reporting[a] according to the Minimum Standard Checklist for evaluating Health related quality of life outcomes in pharmacological trials in CHF.

HRQoL issue	Description
Conceptual	
A priori hypothesis stated	Assessed whether authors had a predefined HRQOL end point and/or stated expected changes because of the specific treatment.
Rationale for instrument reported	Assessed whether authors gave a rationale for using a specific HRQOL measure.
Measurement	
Psychometric properties reported[b]	Assessed whether a previously validated measure was used or psychometric properties were reported or referenced in the article.
Cultural validity verified	Assessed whether the measure was validated for the specific study population.
Adequacy of domains covered	Assessed whether the measure covered, at least, the main HRQOL dimensions relevant for a generic HF population and/or according to the specific research question.
Methodology	
Instrument administration reported	Assessed whether authors specified who and/or in which clinical setting the HRQOL instrument was administered.
Baseline compliance reported[b]	Assessed whether authors reported the number of patients providing an HRQOL assessment before the start of treatment.
Timing of assessment documented	Assessed whether authors specified the HRQOL timing of assessment during the trial.
Missing data documented[b]	Assessed whether authors gave some details on HRQOL missing data during the trial.
Interpretation	
Clinical significance addressed	This refers to the discussion of HRQOL data being clinically significant from a patient's perspective and not simply statistically significant.
Presentation of results in general	Assessed whether authors discussed the HRQOL outcomes, giving any comments regardless of the results (either expected or not).

Adapted from Efficace et al. [9].
HRQoL, health related quality of life; CHF, chronic heart failure.
[a] When multiple instruments were used in a single study only one instrument had to satisfy the item in a checklist to have deemed to have met the health related quality of life issue for that study.
[b] High priority concerns that need to be satisfied.

the Food and Drug Administration (FDA) in the United States (US) request HRQoL data when making drug approval decisions [17]. Including non-pharmacological therapy and devices trials in this review would require additional methodological and reporting issues to be considered [18,19]. This review also sought to investigate whether the methodological and reporting quality of HRQoL outcomes in RCTs have improved over time and as how HRQoL outcome is used in the study (primary vs. secondary outcomes).

2. Methods

A search of the electronic data bases Medline and EMBASE was undertaken with the assistance of a health librarian. The search strategy used relevant keywords and Medical Subject Heading (MeSH) terms including 'heart failure' combined with 'health related quality of life', 'pharmacological therapy' and 'randomized controlled trials' restricted to articles in English (Supplementary material 1). The search was restricted to 1990–2009 as it is in the last 20 years HRQoL has become a research area of interest. RCTs were considered to be eligible if HRQoL was explicitly designated as either primary or secondary endpoint. No restriction was set on type or number of HRQoL assessments in the study. Case reports, editorials, letters, commentaries, reviews, overviews and conference presentations were excluded along with cases where HRQoL assessment was included as a part of a composite endpoint. Studies with insufficient information regarding HRQoL assessment were also excluded. Potentially relevant articles were initially retrieved and if it was deemed appropriate the full text article were sought. Additional relevant studies were identified through a manual search of reference lists from previous review articles [5,14].

The following information was extracted from included studies: Authors, main objective and study interventions, diagnosis, duration of the study, sample size, HRQoL used as primary/secondary outcome, description and type of the HRQoLs used and whether a power calculation was undertaken. When the primary outcome was not explicitly stated by the authors, it was defined as the one that was given prominence in the report or the outcome used for the sample size calculation.

Each RCT was evaluated according to the MSC [9] (Table 1). This checklist facilitates a critical review and interpretation of HRQoL outcomes by addressing the basic and essential issues that a given trial should possess to have sound and reliable HRQoL outcomes in clinical trials [9]. This checklist consists of 11 items grouped into categories addressing basic and essential methodological and reporting issues related to HRQoL assessment in clinical trials: conceptual, measurement, methodology, and interpretation. The items were originally selected from the literature by consensus of HRQoL researchers and further refined by an additional independent panel of 30 experts in the field of HRQoL including clinicians, psychologists and statisticians [9]. Summative scores of eight and over, including three mandatory items (baseline compliance, reporting psychometric properties or referencing validation article and missing data documentation) on this checklist were considered as 'probably robust'. Scores between five and seven or not including all three mandatory items were classified as 'limited' and all other studies were classified as 'very limited'. If more than one HRQoL instrument was used, the study was credited for fulfilling a particular criterion/checklist if it was satisfied by any one of the instruments employed.

To examine the effect of time on the MSC total score for HRQoL outcome, a linear regression model was used with the MSC total score as the dependent variable and the time of publication as the continuous independent variable. Prior to linear regression modelling, correlation analysis was used between MSC total scores, the year of publication, the usage of HRQoL outcome (primary vs. secondary), sample size and the duration of the study in weeks to identify any confounding variables. In addition, the publication year was classified as before and after 2005 to further examine any changes between these two time periods.

3. Results

A total of 392 studies were retrieved. After excluding 256 articles (Fig. 1) not meeting the inclusion criteria 136 studies were included in the review. Of the 136 studies (Supplementary material 2), 73 (53.7%) studies were published from 2000 to 2009. Most studies (n=112; 82.4.4%) used the New York Heart Association (NYHA) class to identify the patient group studied, with the most common grouping being NYHA II–III (46/112; 41.1%) followed by NHHA II–IV (30/112; 26.8%). The reported duration of the study ranged from 1 week to 235 weeks with 54 (40.0%) studies reporting 12 weeks or less. In some studies, this may include a run-in period (Table 2).

HRQoL assessment was described as either a primary or co-primary endpoint in 19 (14.0%) studies (Table 3). However in only 4 of these 19 studies (4/19; 21.1%) the sample size was calculated based on a HRQoL hypothesis or the adequacy of calculated sample size to detect clinically significant HRQoL changes was considered. In more than half of these studies (10/19; 52.6%) a sample size calculation was not reported at all and in five studies (5/19; 26.3%) the sample size calculation was based on the other endpoints. Six of these studies (6/19; 31.6%) were sub-studies of larger RCTs [20–24]. For studies where HRQoL assessment was a secondary endpoint, only four studies (4/117; 3.4%) considered the adequacy of a calculated sample size on HRQoL assessment [25–27] while 64 studies (64/117; 54.7%) did not report on the sample size calculation at all. Of all 136 studies reviewed, 69 (50.7%) studies had a sample size less than 100 patients with the median sample size of 81.5.

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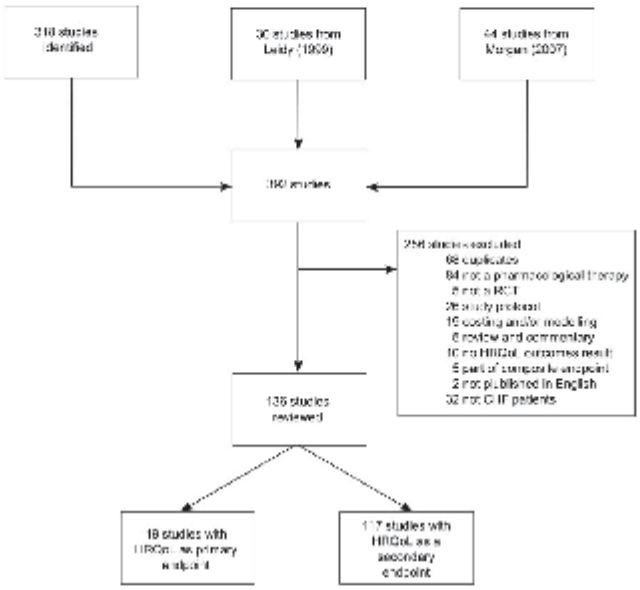

Fig. 1. Flow diagram for study selection.

Although most of studies in this review used a single measure of HRQoL (n = 103; 75.7%), the number of instruments used in a single study ranged from one to five. In cases where multiple measures were used, the most common combination consisted of a condition specific measure and generic measure (9/21, 42.9%). The most commonly used HRQoL measure in CHF trials has been the Minnesota Living With Heart Failure Questionnaire (MLWHF) (n = 83 studies) followed by a generic measure, Global assessment (n = 31 studies where 26 studies were patient provided and 5 studies were provider assessed). In five studies where global assessment was provided by the physician three of these studies also included patient provided HRQoL. The only utility focused measure used in studies in this review was the EQ-5D (n = 6). The results from discrete domains of an instrument were reported in 26 studies (19.1%). Similarly in 33 (24.2%) studies where multiple instruments have been used, results from individual instrument were reported. However, no study reported statistical adjustments for multiple comparisons.

Table 2
Characteristics of the studies included in the review. (n = 136).

Characteristics	n (%)
Sample size	
≤50	49 (36.0)
51–100	20 (14.7)
101–150	14 (10.3)
151–200	7 (5.1)
201–250	9 (6.6)
≥251	37 (27.2)[b]
Study duration (in weeks)[a]	
≤12 weeks	54 (40.0)
13–24 weeks	24 (17.8)
25–36 weeks	18 (13.3)
37–48 weeks	5 (3.7)
≥49 weeks	34 (25.2)
No. of questionnaire used per study	
1	103 (75.7)
2	14 (10.3)
≥3	19 (14.0)

[a] One study did not specify time frame.
[b] Percentages do not add to 100% due to rounding error.

3.1. Minimum standard checklist

Overall, 83 (61.0%) studies reported an a priori hypothesis or had a predefined HRQoL endpoint (Table 4). The rationale for instrument selection was reported in 34 (25.0%) studies. Eighty-six (63.2%) studies provided psychometric properties of the instrument used or cited the validation study. Interestingly, although 12 (8.8%) studies stated that the HRQoL instrument was developed for the purpose of their study, none of these studies reported the psychometric properties of the instrument or cited the source of a validation process. In 38 (27.9%) studies it was unclear whether the instrument was developed for the study or the authors were using an already established instrument.

While only 55 (40.4%) studies specified who and/or in which clinical setting the HRQoL instrument was administered, most of the studies (n = 130; 95.6%) documented the timing of HRQoL assessment. Although 107 (78.7%) studies discussed the general result of HRQoL outcome in their discussion, only 57 (41.9%) studies addressed the clinical significance of the HRQoL outcomes. Only 23 (16.9%) studies satisfied all three mandatory items of MSC. According to the MSC, 26 (19.1%) studies were considered 'very limited' in methodological and reporting of HRQoL results and 91 (66.9%) studies were evaluated as 'limited'. Only 19 (14.0%) studies were considered to be 'probably robust'.

Correlation analysis demonstrated that no confounding variables were present. A linear regression analysis showed the absence of a significant time effect on the MSC scores ($\beta = 0.025$; $p = 0.775$). The percentage of studies judged as 'probably robust' was 14.9% for those published between 2005 and 2009 and 13.5% for those published earlier (Table 4). A similar pattern was observed in the 'limited' and 'very limited' groups. In fact, the only MSC item that has

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Table 3
Characteristics of studies with health related quality of life as a primary/co-primary endpoint. (n = 19).

Authors	Year	Main objective	Patient group description	Sample size[a]	Intervention	Study duration[b]	HRQoL instrument	Power calc.	MSC class
Baligadoo et al. [42]	1990	To assess the effect of an inotropic agent on quality of life	NYHA III	10	Oral enoximone 150 mg tds or PL	3 weeks	Disease specific HRQoL[c]	None	Limited
Rector et al. [43]	1993	To determine if the patients' perceptions of the effects of enalapril on their daily activities and sense of well-being were different from those of a group treated with hydralazine and isosorbide dinitrate.	NYHA I–III	804	Enalapril or Hydralazine and Isosorbide dinitrate	216 weeks	MLWHF	None	Probably robust
Ekelberg et al. [21]	1994	To test the hypothesis that treatment with the ACE inhibitor enalapril is associated with a quality of life similar to that on placebo	4–6 months after myocardial infarction	132	Enalapril	26 weeks	Nottingham Health Profile Physical Symptoms Distress Index Work Performance Scale Life Satisfaction Index	None	Limited
Rogers et al. [23]	1994	To assess the quality of life of patients with left ventricular dysfunction for up to 2 years after randomization to enalapril or placebo	EF ≤ 0.35	5025	Enalapril ≤ 10 mg or PL	104 weeks	Scales excerpted from validated instruments (POM, Functional Status Questionnaire, SF-36)	None	Probably robust
Cohn et al. [44]	1997	To describe the response of quality of life to vasodilating beta-blocker carvedilol in the subset of patients with the most severe impairment of exercise capacity	NYHA III–IV	131	Vasodilating beta-blocker carvedilol or PL	26 weeks	MLWHF	On HRQoL	Probably robust
Doroszewski et al. [45]	1997	To assess the effects of ungapidil combined therapy on QoL, exercise tolerance and haemodynamic parameters	NYHA III–IV	36	Urapidil or PL	12 weeks	Modified MLWHF	On other endpoint	Limited
Bolight et al [46]	1998	To measure quality of life (QOL) in patients with mild to moderate heart failure treated with angiotensin converting enzyme (ACE) inhibitors cilazapril or captopril.	NYHA II–IV	367	Angiotensin converting enzyme (ACE) inhibitors cilazapril or captopril	24 weeks	SIP POM Mahler Index of dyspnea-fatigue (Provider supplied) Health status index	On other endpoint	Probably robust
Newby et al [47]	1998	To assess the effect of candoxatilat exercise capacity, clinical status and quality of life in patients with mild to moderate chronic heart failure receiving angiotensin converting enzyme inhibition.	NYHA I–III	190	Candoxatil or PL	12 weeks	Questionnaire assessing breathlessness, fatigue and well-being[d]	None	Limited
Sanderson et al. [48]	1999	To compare the long-term clinical efficacy of treatment with metoprolol versus carvedilol	NYHA II–IV	51	Metoprolol or Carvedilol	12 weeks	MLWHF	On HRQoL	Limited
Cowley et al. [20]	2000	To measure health-related quality-of-life (HRQoL) in elderly symptomatic heart failure patients following treatment with an angiotensin II receptor antagonist (losartan) vs an angiotensin-converting-enzyme (ACE) inhibitor (captopril)	NYHA II–IV	203	Losartan or Captopril	48 weeks	MLWHF SIP	On other endpoint	Probably robust
Fung et al. [49]	2002	To compare the effectiveness of beta blockade in patients with heart failure and AF using MLWHF as a symptom measure	NYHA II–IV	63	Metoprolol 50 mg twice daily or carvedilol 25 mg twice daily in addition to standard therapy	12 weeks	MLWHF	On other endpoint	Limited

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Lader et al. [24]	2003	To evaluate the effect of digoxin therapy on HRQoL	NYHA I–IV	580	Digoxin therapy	52 weeks	SF-36 Ladder of Life CES-D State Anxiety Inventory State Anger Inventory MLWHF	None		Probably robust
Lopez-Candales et al. [30]	2004	To investigate the need for hospice and palliative care programs among patients in end-stage heart failure who receive intermittent infusion of inotropes with MLWHF as a primary endpoint.	NYHA III–IV	73	Inotrope or PL	Unknown	MLWHF	None		Limited
Majani et al. [22]	2005	To examine the effect on quality of life (QOL) of valsartan administered in addition to prescribed background heart failure therapy	NYHA II–IV	3010	Valsartan (160 mg twice daily) or placebo in addition to prescribed background therapy (beta-blockers or angiotensin-converting enzyme inhibitors)	196 weeks	MLWHF	None		Probably robust
Rajendran et al. [51]	2005	To compare the conventional with individualized digoxin dosing on quality of life and other various clinical outcome		41		52 weeks	MLWHF	None		Limited
Parissis et al. [52]	2007	To investigate the impact of levosimendan on QoL, physical activity and emotional stress in patients with severe CHF	NYHA III–IV	63	24 h levosimendan infusion or Placebo		KCCQ DASI BDI SDS	None		Limited
Kourea et al. [53]	2008	To investigate the effects of recombinant human erythropoietin analog darbepoetin-a on quality of life and emotional stress	NYHA II–III	41	Darbepoietin-a plus iron or Placebo plus iron	12 weeks	KCCQ DASI BDI SDS	Post power calculation on KCCQ		Limited
Yip et al. [54]	2008	To asess the effects of delapril conagred with captopril on quality of life, symptoms and LV global and regional function	LVEF>45%	150	(1) diuretics alone, (2) diuretics plus irbesartan, or (3) diuretics plus ramipril	52 weeks	MLWHF	On other endpoint		Limited
Fonarow et al. [55]	2009	To evaluate the effects of orally administered L-arginine in CHF patients on quality of life, 6x minute walking tests and complete Doppler and echocardiographic evaluation.	NYHA II–III	68	L-arginine or Placebo	12 weeks	MLWHF	On HRQoL		Probably robust

HRQoL, Health Related Quality of Life; MSC, Minimal Standard Checklist; PL, Placebo; CES-D, Center for Epidemiological Studies Depression Scale; MLWHF, Minnesota Living with Heart Failure Questionnaire; POMS, Profile of Mood States; SF-36, Medical Outcomes 36-Item Short-Form General Health Survey; SIP, Sickness Impact Profile; KCCQ, Kansas City Cardiomyopathy Questionnaire; DASI, Duke's Activity Status Index; BDI, Beck Depression Inventory; SDS, Zung Self-rating Depression Scale.

[a] As reported in the paper (this may be the number of patients recruited, the number of patients who completed the study, or the number of patients who have completed health related quality of life assessments).

[b] As reported in the paper (this may include a run-in period).

[c] Author developed.

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Table 4
Level of reporting[a] according to the (adapted)[b] MSC for evaluating HRQoL outcomes in CHF pharmacological trials by the duration of study period and by use of HRQoL endpoint.

	Publication year		HRQoL endpoint		Total
	n (%)		n (%)		
MSC standard checklist	1990–2004 (n = 89)	2005–2009 (n = 47)	Primary (n = 19)	Secondary (n = 117)	(n = 136)
Conceptual					
A priori hypothesis stated	52 (58.4)	31 (66.0)	18 (94.7)	65 (55.6)	83 (61.0)
Rationale for instrument reported	17 (19.1)	17 (36.2)	7 (36.8)	27 (23.1)	34 (25.0)
Measurement					
Psychometric properties reported	56 (62.9)	30 (63.8)	15 (78.9)	71 (60.7)	86 (63.2)
Adequacy of domains covered	70 (78.7)	42 (89.4)	18 (94.7)	88 (75.2)	112 (82.4)
Methodology					
Instrument administration reported	38 (42.7)	17 (36.2)	13 (68.4)	42 (35.9)	55 (40.4)
Baseline compliance reported	41 (46.1)	19 (40.4)	12 (63.2)	48 (41.0)	60 (44.1)
Timing of assessment documented	86 (96.6)	44 (93.6)	18 (94.7)	112 (95.7)	130 (95.6)
Missing data documented	44 (49.4)	17 (36.2)	12 (63.2)	49 (41.9)	61 (44.9)
Interpretation					
Clinical significance addressed	37 (41.6)	20 (42.6)	17 (89.5)	40 (34.2)	57 (41.9)
Presentation of results in general	71 (79.8)	36 (76.6)	19 (100.0)	88 (75.2)	107 (78.7)
Checklist score					
Very limited	17 (19.1)	9 (19.1)	0 (0.0)	26 (22.2)	26 (19.1)
Limited	60 (67.4)	31 (66.0)	11 (57.9)	80 (68.4)	91 (66.9)
Probably robust[c]	12 (13.5)	7 (14.9)	8 (42.1)	11 (9.4)	19 (14.0)

MSC indicates Minimum Standard Checklist; HRQoL, Health related quality of life; and CHF, Chronic heart failure.
[a] When multiple instruments were used in a single study only one instrument had to satisfy the item in a checklist to have deemed to have met the HRQoL issue for that study.
[b] An issue relating to 'Cultural validity verified' on the checklist has been omitted.
[c] Including three mandatory items; baseline compliance reported, missing data and psychometric properties documented or referenced.

improved significantly over time was 'rationale for instrument selection'; 36.2% (17/47) of those studies published between 2005 and 2009 compared to 19.2% (17/89) of the studies published earlier provided the rationale.

Quality of reporting on HRQoL was higher in the trials with HRQoL as a primary/co-primary endpoint (Table 4). These trials were more likely to report an a priori hypothesis (94.7% vs. 55.6%), the clinical setting in which HRQoL instrument was administered (68.4% vs. 35.9%), and to discuss the clinical implication of the result (89.5% vs. 34.2%). According to the MSC, while 42.1% (8/11) of the studies with HRQoL as a primary/co-primary endpoint were considered 'probably robust', the percentage was much lower for the studies with HRQoL as a secondary endpoint (9.4%, 11/117). Of the studies with HRQoL as a primary/co-primary endpoint, the remaining 57.9% (11/19) of the studies were evaluated as 'limited' with none being 'very limited'. However, 22.2% (26/117) of the studies with HRQoL as a secondary endpoint were 'very limited'.

4. Discussion

Although HRQoL assessments have the potential to provide a meaningful and clinically relevant outcome of a disease and the effects of pharmacological therapy from the patient's perspective, our analysis reveals that the methodological and reporting rigor of HRQoL assessment in these RCTs has been less rigorous than reporting standards in cancer [28]. Only 14.0% of the studies can be described as 'probably robust'. This compromises the value of such data.

In some studies the researchers did not provide an operational definition of HRQoL and the ambiguity of this constructed has been previously noted [10]. Subsequently, there was no description of how the multidimensional concept of HRQoL including physical, psychological and social domains was measured. In fact, in some studies the terms "HRQoL" and "physical functioning" and/or "symptoms/side effects" were used interchangeably from study question to methods to discussion. For example, in a study the research question may specifically address only one dimension of HRQoL such as physical functioning but in the discussion the term HRQoL would be used, or a study question may refer to HRQoL but only one dimension of HRQoL such as symptom burden was actually measured. This confusion and ambiguity has been previously reported [29]. Although the summative HRQoL score is influenced by each domain, these domains in isolation do not constitute a comprehensive assessment of HRQoL. Therefore, extreme caution is required in drawing conclusions about HRQoL benefits when the assessment is based on the interpretation of results from a limited number of domains [8]. Furthermore, using a subset of an existing instrument may compromise the integrity of the psychometric properties of the original instrument [30]. Consequently, the use of the term HRQoL should be avoided when the study question only addresses one dimension of the concept or vice versa [29].

In this review, 61.0% of the studies stated an a priori hypothesis (or had predefined HRQoL endpoints) although only 25.0% provided the rationale for the choice of the HRQoL instrument. This is an important issue as an a priori hypothesis and the choice of a specific HRQoL instrument are interwoven [31]. The choice of HRQoL instrument in a study should be determined by the severity and nature of the disease as well as expected benefits and side effects of the treatment. Consequently, the a priori hypothesis should indicate which aspects of HRQoL are measures of interest and likely to be affected by the treatment under consideration [32]. This will ensure that an appropriate, relevant, valid and responsive instrument will be used for the study [33]. By reporting on these conceptual issues, the consumers of research can critically examine the extent to which the selected instrument covers the research question.

Although more than half of the reviewed studies used an existing instrument, only 63.2% of the studies reported psychometric properties or referenced the validation study. This raises a question about the validity, reliability, responsiveness, sensitivity and appropriateness of the HRQoL outcomes in the remaining studies (36.8%). In addition neglecting to report on psychometric properties of the instrument may also compromise the ability to critique whether the HRQoL instrument is reliable and valid. In this review, 95.6% of the studies documented the timing of HRQoL assessment but only 40.4% of the studies reported on the method of HRQoL instrument administration. These issues are essential in interpreting study data.

In almost half of the studies, the reported duration of the study was 12 weeks (3 months) or less. The timing of assessment is important especially when evaluating an outcome such as HRQoL. In most

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situations, following a baseline assessment, a sufficient length of time may be required before HRQoL changes occur and this may be different from the time for clinical changes to appear. Incorrect timing of HRQoL assessments could potentially jeopardize the reliability and the validity of the HRQoL findings [34]. Erroneous findings may result due to possible confounding of the treatment effect on HRQoL assessment with the differential effects in assessment timing. If the treatment effect was measured on a HRQoL instrument outside an accepted time window the result may be different. Choosing appropriate timing of HRQoL assessment must be considered carefully to ascertain possible transient effects of treatment on HRQoL.

Only 44.9% of the studies in this review documented missing data and 44.1% reported on baseline compliance. This is an important issue especially in studies of elderly patients with CHF. In such studies, patients often drop out of the study because of severe illness or even death. This may lead to selective loss of information and hence a bias may be introduced. Moreover, the most pertinent HRQoL results could possibly be obtained from patients who may not complete the trial [8]. In addition, this loss of information would reduce the sample size and/or information, hence the ability to detect clinically meaningful differences. Consequently, it is critical to provide information on strategies used to minimize HRQoL missing data and/or at least acknowledge how they were managed to increase validity of HRQoL results. This will aid interpreting HRQoL result.

In this review, few studies with HRQoL as a primary/co-primary endpoint reported sample size based on a HRQoL hypothesis or considered the adequacy of the agreed sample size on HRQoL assessment. In addition, almost half of the studies had a sample size less than 100 patients. All of these studies may have been inadequately powered to detect clinically important differences in HRQoL scores and this was acknowledged in some of the reports. It has been suggested that even when HRQoL assessment is a secondary endpoint and hence power calculation is not expected, some a priori hypotheses should be made concerning the expected changes in HRQoL scores either as an effect size or minimal important differences for agreed sample size [8]. This assessment will assist in eliminating the disparity between clinical and statistical significance [33].

Most of the studies in this review reported on multiple HRQoL comparisons between different time points or/and using multiple instruments. These can potentially increase the proportion of missing data and false positive results caused by multiple comparisons without appropriate statistical adjustments [35]. Consequently numerous approaches have been suggested to minimize this risk such as comparing only the summary score, adjusting p values, or to analyze only selected domains [8,35]. However, all of these approaches will place limitations on the interpretation of the results and caution should be exercised in drawing conclusions from such HRQoL results. Furthermore, most of the studies did not specify in the a priori hypothesis whether the comparisons were made between treatment arms after randomization or with their respective baseline scores obtained at randomization. There is clearly a need for the consensus on the most relevant way to analyze longitudinal HRQoL data [31].

In a systematic review [36] of the generic quality of life questionnaire, the Medical Outcome Study Short Form Health Survey, SF-36, the authors concluded that quality of life outcomes in clinical trials are frequently underestimated and often overlooked.

Despite a dearth of information on improving methodological and reporting quality of HRQoL outcomes [8,37,38], the reporting quality of HRQoL in CHF pharmacological therapy RCTs has not improved over time. In this study this trend was noted in all items in MSC checklist except for 'rationale for selecting a specific HRQoL questionnaire'. While few studies published before 2005 addressed this issue the studies published more recently showed higher compliance. This may be due to the US FDA requiring support for the labeling treatment benefit claim when making drug approval decision [39]. As expected, quality of reporting of HRQoL was superior in trials with HRQoL as a primary/co-primary endpoint.

Efforts, especially in oncology, to improve HRQoL assessment and reporting in clinical trials have seen a major improvement [28]. The reasons suggested for this improvement are the development of specific guidelines and checklists for reviewing and facilitating the critical appraisals and interpretation of HRQoL outcomes [40]. A lack of familiarity regarding psychometric considerations of HRQoL measurement issues may contribute to inadequate reporting [28]. Developing and adopting similar guidelines and checklists in CHF may lead to an improvement in reporting.

4.1. Limitations

There are some potential limitations to this review. Despite the search strategy using two literature databases, the criteria for this review may have omitted some relevant and important studies especially in non-pharmacological and device trials. However the purpose of the study was to review the methodological and reporting rigor in HRQoL assessment using pharmacological therapy as an exemplar. This review did not take into account unpublished reports and the scarce details in some articles that have limited their usability in this review. Although issues addressed in terms of design and methods of measurement of HRQoL discussed in this review were limited to pharmacological trials, important HRQoL methodological issues in analysis, presenting and interpreting results could be applicable to other RCTs in CHF.

This review did not assess the overall quality of the trial but only the methodological and reporting quality of HRQoL assessment in the trials. Furthermore, some methodological deficiencies may lie in the reporting (or not reporting) rather than in their performance. In addition, this review did not evaluate the appropriateness or the importance of HRQoL as an outcome in clinical trials or the quality of the validation of the HRQoL instruments used. Although the MSC was developed in oncology, critical HRQoL assessment issues addressed in the checklist were adapted in this review for CHF. Using other criteria, the studies could have been categorized somewhat differently. Furthermore, by summarizing the 11 items in MSC quality criteria into one overall score may have weighted all items as equally important, which may not be the case.

4.2. Conclusion

Although HRQoL is an important clinical endpoint with a potential to influence clinical decision making, evidence to date has shown a limited impact of HRQoL on patient management [7]. This may be due to clinicians' skepticism as to the validity of HRQoL. To date few studies reporting HRQoL in CHF were deemed 'probably robust' using validated criteria. Refining guidelines and checklists for the assessment of HRQoL outcomes in CHF clinical trials is warranted and is currently being developed by the Consolidated Standards of Reporting Trials (CONSORT) group [41].

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Conflict of interest

None declared.

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Review

Health span or life span: The role of patient-reported outcomes in informing health policy

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ABSTRACT

Objectives: Population ageing and the increasing burden of chronic conditions challenge traditional metrics of assessing the efficacy of health care interventions and as a consequence policy and planning. Using chronic heart failure (CHF) as an exemplar this manuscript seeks to describe the importance of patient-reported outcomes to inform policy decisions.
Methods: The method of an integrative review has been used to identify patient-reported outcomes (PROs) in assessing CHF outcomes. Using the Innovative Care for Chronic Conditions the case for developing a metric to incorporate PROs in policy planning, implementation and evaluation is made.
Results: In spite of the increasing use of PROs in assessing CHF outcomes, their incorporation in the policy domain is limited.
Conclusions: Effective policy and planning is of health care services is dependent on the impact on the individual and their families. Epidemiological transitions and evolving treatment paradigms challenge traditional metrics of morbidity and mortality underscoring the importance of assessing PROs.

Contents

1. Introduction

Ageing and the increasing burden of non-communicable diseases is influencing strategic policy initiatives in both developed and developing countries [1]. These factors also challenge clinicians and policy makers to consider health and social outcomes beyond traditional concepts of morbidity and mortality. Rapidly growing disciplines, such as health economics strive to balance parameters of demands, costs, and benefits relative to patient outcomes and treatment allocation [2,3].

Clinicians and policy makers are more aware of the complex interplay of social, economic, physiological and policy factors in determining health outcomes [4–6]. The

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dilemmas confronting contemporary society underscore the need to increase the links between researchers and policy makers to develop, evaluate and implement appropriate interventions [7]. As well as assessing clinical outcomes, we also need to capture the unique perspective of the individual and their social determinants of health, to effectively inform health care planning [8]. This is of particular significance in chronic and aged care conditions where psychological and social issues play an important role in etiology and prognosis [9,10]. Balancing treatment burden in the elderly is of concern and often gains in longevity are not matched by symptom relief and quality of life [11]. The health status of a population has traditionally been measured in terms of mortality and morbidity rates. Yet, with the epidemiologic transition from infectious to chronic diseases, quantifying health in terms of death and disease rates is seen to be increasingly inadequate [12]. Moreover, the ageing of the population means that a greater proportion of the population will receive treatment for chronic disease for a longer period of time. In chronic diseases, the goal of treatment commonly changes from cure to control of symptoms through targeted interventions.

1.1. Patient-reported outcomes

The increasing complexity of treatment allocation, acceptability and utility makes the views of consumers more critical in intervention development, evaluation and health service planning [13]. One way to achieve this perspective is through assessing patient-reported outcomes (PROs). This term refers to information and measures reported directly by the individual affected by a health condition, treatment or life experience [14]. Further, PROs is an umbrella term to capture the patient's subjective perceptions of the broad spectrum of disease and treatment outcomes. Health-related quality of life (HRQoL) is one of several types of PROs. Others include subjective symptoms, functional status, psychological well-being, treatment adherence, and satisfaction with treatment. For example, capturing information to bathe without assistance and participate in activities of daily living is important in determining the impact of an intervention. Further, if an individual is unable to either fill their medication prescription or open the medication container – pharmacotherapy is unlikely to be effective. Patient-reported outcomes can be either generic or specific to a clinical condition or disease state. Often the term "PROs" has been used to refer to the concept being measured, the instrument used to measure that concept and the actual endpoint. There is a need to distinguish the concept and outcome one is attempting to measure and the endpoint for statistical analysis [15]. It is vital to have sufficient evidence that PRO concept is adequately measured by a PRO instrument [16]. In recent decades there has been an exponential growth in the measures and it is important to consider not only the psychometric properties but also the utility in making treatment decisions and policy development.

Despite benefits of a proposed treatment there is also the risk of intervention having deleterious effects on the individual's quality of life and capacity to undertake activities of daily living. In such a case, the cure can be worse than the disease. Likewise, extended life can mean living for a prolonged period with a disability [17]. As complexity, burden and cost of treatment escalates, it is vital that patients and their families, clinicians, policy makers and funding bodies have a realistic expectation of outcomes, not merely in relation to the physical, but from a psychological and social dimension as well [18]. Gathering the unique perspective of patients and their families is paramount. These data will be crucial in informing policy makers need to plan and implement strategic initiatives.

Therefore it is increasingly an important consideration that the unique perspective of the patient be represented in not only individual clinical encounters, including patient assessment, but also in health policy, clinical trials and health service evaluation [19].

The Innovative Care for Chronic Conditions (ICCC) framework (Fig. 1) has been developed to help reorient

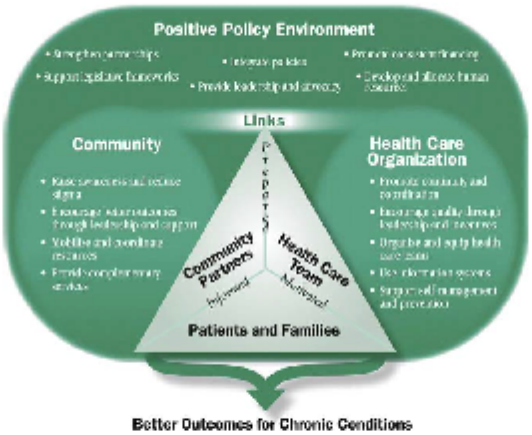

Fig. 1. The Innovative Care for Chronic Conditions(ICCC)framework.

health care systems to manage the demands of the rising burden of chronic conditions around the world [20]. At the centre of the framework is the health care triad (micro-level of care); the partnership between patients and families, health care teams, and community supporters. To achieve optimal outcomes this triad needs to be supported by the broader community and the integrated health care organisations (meso-level of care). This in turn needs to influence the broader Positive Policy Framework (macro-level of care) and to be influenced by them. It is contingent on every member of triad (patients and families, health care teams, and community supporters) being informed, and to maintain communication and collaboration. The ICCC framework emphasizes the importance of patients and families, forming one-third of the key 'partnership triad' at the most basic level. Furthermore, because management of chronic conditions requires lifestyle and daily behaviour changes, emphasis needs to be placed on the patient's central role and responsibility in health care. When we refer to the patient, we consider family members and carers as part of this unit. Inclusion of this important dimension is contingent upon developing and testing of a model to measure the patient's unique perspective.

In order to provide a more in depth discussion of the notion of PROs and how these can inform the metric that assists policy makers in developing and implementing health policy, we have chosen heart failure (HF) as an exemplar of a chronic condition [21]. Heart failure is a disabling and progressive condition and is the end stage of most heart disease. The unpredictability and severity of physical symptoms such as dyspnea, fatigue and pedal edema has led to great deal of anxiety and fear in patients living with heart failure [22]. Numerous studies have also shown that HF is associated with depression, and that this association is linked with a worse prognosis [23]. In studies with comparative normative data the degree of physical, mental and social functioning impairment was greater in heart failure patients than other chronic diseases sufferers [24,25]. In fact, many patients with advanced heart failure ascribe greater importance to quality than to duration of life which may be limited by heart failure [26]. Furthermore, HF is the leading cause of hospitalisation in industrialised countries [27] with high readmission rates [28] and prolonged length of stay which all lead to an increasing burden on resources both personally for patients, and financially for health care services [29]. In developed countries it accounts for 1–2% of all health care expenditure [30].

Heart failure is primarily a condition of ageing. As treatment of hypertension, acute myocardial infarction and valvular disorders has met with increasing success, the incidence and prevalence of heart failure has increased dramatically. The prevalence of HF has been shown to increase from less than 1% in the 20–39 years to over 20% in 80 years and older [31]. In addition the incidence of heart failure doubles between 65–74 years and 75–84 age bands [32]. Increasingly, ethical and treatment conundrums arise out of the need to accurately assess the wishes of patients and their families and further tailor services to meet the needs of the vulnerable elderly [33,34].

A diagnosis of HF presents many of the challenges associated in caring for the elderly with a chronic condition from the perspective of the individual with the condition, their family and carers, as well as health professionals and the systems to support them [35]. Namely, it is a recurrent, costly and resource intensive chronic condition with an illness trajectory punctuated by episodes of decompensation and poor prognosis [36]. In spite of extensive evidence, there is evidence of a treatment gap that necessitates researchers, clinicians, administrators and policy makers to collaborate on strategies to achieve an evidence-based approach to health care [37]. Equally, we are aware that some treatments may impact adversely on patients' perception of quality of life in spite of improving more traditional endpoints such as mortality. It is important to remember that the definition of evidence-based health care relates not only to the best practice treatments, but the administration of these in accordance with the patient's values and preferences [38]. Although substantive literature exists in discrete categories, such as quality of life and health service evaluation, there is considerably less experience in the integration and synthesis of this information to provide an outcome measurement model that takes into consideration clinical, organisational and patient factors [39].

As discussed above, PROs in the context of health care have become an increasingly important focus of regulatory bodies and health care administrators [18]. The potential for interventions and treatments to be assessed from the perspective of the patient through validated psychometric measures is a critical issue for clinical practice, outcome evaluation and research. At a conference to assess the contribution of the Agency for Health Care Policy and Research (AHCPR) in enhancing outcomes, it was concluded that researchers and policy makers need to build upon descriptive studies and methodological advancements with the goal of measurably improving outcomes, quality, and efficiency of care [40]. Developing this science is dependent upon collaboration between consumers, academics and clinicians from a range of disciplines as well as policy makers and administrators.

2. Materials and methods

An integrative review was undertaken to summarize how PROs have been defined, measured, and used in chronic heart failure research and identify their possible implications for policy initiative. We searched the electronic databases CINAHL, Medline, Embase and the Internet were searched using key words including 'heart failure', 'instruments', 'psychometric instruments' and 'patient-reported outcomes.' Furthermore the reference lists of published materials were hand searched for additional data sources. The aim of the review was to explore PRO measures in CHF that may provide new insight in policy decisions. A range of measures contributing to the impact of the outcomes of CHF, such as medication adherence and self-management were explored. Inclusion criteria were those papers that explored PROs measures that would provide new dimension in outcomes of CHF. Exclusion criteria were papers not published in English. Abstracts were appraised that most fitted the aims of the review and met the inclusion criteria.

Table 1
Examples of patient-reported outcome in chronic heart failure.

Construct	Definition	Disease specific examples	The impact of CHF on an individual
Health-related quality of life (HRQoL)	HRQoL concerns attributes of life valued by patients, such as level of comfort; sense of well-being; ability to maintain reasonable physical, emotional, and intellectual function; and ability to participate in valued activities [58]	Examples of disease specific instruments include the Minnesota Living with Heart Failure Questionnaire [59], the Chronic Heart Failure Questionnaire (CHQ) [60] and the quality of life questionnaire in severe heart failure (QLQ-SHF) [61], Kansas City Questionnaire [62]	Patients with CHF often experience a burden of disease that has a negative effect upon their health-related quality of life. The important goal of increasing the length of healthy life demonstrates a change from just measuring mortality and morbidity to also include health-related quality of life (find reference in CHF patients)
Self-reported functional status	Self-reported functional capacity or status usually refers to ability to participate in everyday activities, in distinction to psychological aspects of quality of life such as perception of health [63]	Self-reported functional status in heart failure patients is usually assessed by using subscales of quality of life questionnaires [61]	How much symptoms (and psychologic distress) commonly associated with heart failure limit physical, social, role, and mental function. It also incorporates the effects of extraneous factors such as personal motivation and comorbidity which may not be able to be captured by clinical outcomes [64]
Psychological distress	Psychologic distress refers to feelings of dysphoria, anxiousness, worry, and other negative psychologic reactions to illness ([64])	A variety of self-report and interview measures have been used to assess levels of depression in CHF including a range of generic instruments. The CDS is a self-report, 26-item self-rating scale, which measures depression specifically in cardiac patients and may be used to measure depression in patients with heart failure [65]. However, it should be noted that somatic depression symptoms of fatigue and insomnia included in the CDS are also primary symptoms of CHF	It is only recently that attention to the psychosocial issues of CHF including stress, anxiety and depression had increased. These factors have been related to coping styles and physical health of patients with CHF. Besides predicting cardiac events and affecting mortality, it is possible that depression may contribute to the high readmission rates for patients with CHF [66,67]
Spiritual/existential	Reference to spiritual and existential issues refers to the search for meaning, purpose and fulfilment in life [68,69]	Spirituality in HF patients is assessed by Spirituality Assessment Scale (SAS), which is a generic instrument or using a qualitative method which allows a deep understanding of the social and illness experience of HF patients [70]	Spiritual beliefs serve as a buffer for stressful physical and emotional events associated with chronic illness in HF patients [71]. Spirituality has also been linked with the adjustment of patients with severe heart failure [69]
Self-care	Self-care involves a process of maintaining health through positive health practices, and managing illness and disease [72]. Patients with a chronic illness such as heart failure engage in self-care primarily to manage what may be a precarious balance between relative health and symptomatic heart failure	Self-Management of Heart Failure instrument developed by Riegel et al. for evaluating the self-management abilities of HF patients [73]	Self-care can have positive lifestyle modification effect, on response to worsening symptoms and on coping with chronic illness [74]. All of these will lead to fewer problems leading to readmission or unnecessary visits to emergency department [74]
Self-efficacy	Self-efficacy is the judgment that individuals develop about their own ability to successfully perform a given behaviour	The Heart Failure Self-Efficacy Scale–30 (HFSE-34) is a disease specific instrument and contains five subscales designed to measure self-efficacy with medications, diet, symptom control, and activity and HF readmissions [75]	Self-efficacy has been demonstrated to be a marker of cardiac function and has been demonstrated to predict mortality and hospitalisation [76]. Self-efficacy is increasingly used as a predictor of behaviour and adherence [77]
Satisfaction	Satisfaction can be defined as the extent to which individuals perceive either positively or negatively the impact or delivery of a health intervention [78,79]	There are no disease specific, prevalent, systematic, or statistically validated instruments for measuring patient satisfaction with heart failure. Patient satisfaction has been measured only as a part of a battery of "outcome" measures, such as quality of life or health need assessment or satisfaction of particular interventions such as video-consultations [80,81]	Patient satisfactions can be used as an endpoint that explores affability, accessibility and availability of high quality care [82]

Table 1 (Continued)

Construct	Definition	Disease specific examples	The impact of CHF on an individual
Treatment adherence	Adherence is defined as the extent to which a person's behaviour coincides with medical advice. It is a multifactorial process involving characteristics of the health care system, the individual, the treatment regimen characteristics, and the quality of the patient–provider interaction [83,84]	The HF Compliance Questionnaire (HFCQ) and its revised version (The HFCQR) have been used to measure patients' adherence to medical regimen [85]	Poor treatment compliance among HF patients has been linked to increased mortality and morbidity rates and increased health care costs associated with increased outpatients care as well as hospital readmission [84]
Cognitive status	Cognition refers to those mental activities associated with thinking, learning, and memory. There is strong evidence to suggest multiple contributors to cognitive dysfunction in CHF [86]	Increasingly validated measures of cognitive function, particularly those assessing executive functioning are used in CHF [87]	It is estimated 25–50% of HF patients have cognitive impairment [86]. HF has been proposed a s a possible cause of cognitive function, expressed as a term 'cardiogenic dementia' [88]
Social support	Social support refers to the perception of both instrumental support and assistance psychologically and emotionally [89,90]	Social support has been assessed in CHF and identified as a predictor of outcome [91]	Social support influences symptoms and functional status, health [perceptions [91]]. It would facilitate management of symptoms such as fatigue and cognitive impairment [58]
Carer outcomes	Carers play a critical role in supporting individuals with CHF and this can have both positive and negative health, social and psychological outcomes [92]	A number of caregiver instruments are available to assess caregiver outcomes [93]	Caregivers play an important role in the care of patients with HF, hence caregiver contributes to patient outcomes [94]. Lack of caregiver support has been shown to be associated with higher rates of hospitalisations for patients with heart failure [94]
Social capital	Social capital relates to networks and relationships in society based upon normative values that enable collaborative and cooperative activities for mutually beneficial outcomes [95]	The issue of how social capital is lined to health and disease including heart failure remains uncertain although the strong association between social determinants of health and outcomes make this of an increasing interest and concern [96]	Social capital is associated with quality of life especially in an old age [97]. Also social capital has been shown to be linked to health care utilisation and demand [98]
Resilience	Resiliency refers to a person successfully adapting to adverse life events or circumstances or both [99]	Resilience of the patient to CHF is poorly studied, although hope has been described [100]	Resilience would minimise demoralisation, depression and vulnerability in CHF patients [43]
Needs	Needs assessment is a tool for evaluating perceptions of health status, determining patient satisfaction and treatment plans [39]	Nottingham Health Needs Assessment (NHNA) has been designed to specifically assess the health needs of cardiac patients [101]. The Heart Failure Needs Assessment Questionnaire has also been developed specifically for individuals with CHF [39]	Provides information on patients' perceptions of their existing health status and unmet needs in current management plan [39]. Guides planning and projection of needs of patients and population [39]

Examples of commonly used PROs are provided to illustrate the importance of including these issues in policy decisions. Table 1 provides examples of these constructs that assess the impact of CHF on an individual, ranging from limiting activities of daily living through to existential distress. Although this list is not exhaustive it provides insight into the range of measures available. Despite many potential uses of PRO measures in CHF, the primary area of application has been in randomised clinical trial investigation, particularly HRQOL. This is in line with the recognition that the changes in physiological measures may not always translate into a tangible benefits perceived by the patients. In closer inspection of these measures, outcomes important to patients are affected not only by symptoms and disease severity but also by a complex interaction of physical, social and psychological factors. By incorporating patients' perspective they account for differences, subjective as well as objective among individual patients and to cater for patient's preference. When the individual is unable to complete such measures, the use of proxies can be considered.

Importantly, PROs extend beyond traditional clinical efficacy and adverse effects and represent the patient's perspective on the impact of disease and its treatment on daily functioning and well-being [41]. In many situations patient report is the sole source of data on frequency and severity of symptoms and also the side effects and the impact of treatment on functioning and well-being [42]. Hence they are managed and monitored almost entirely on patient reports. Indeed in conditions where there are no physical or physiological markers of disease activity, PROs become the outcome of choice for evaluating disease activity and

in providing comprehensive understanding of severity of symptoms and their impact on daily functioning and well-being. Palliative and supportive care is a striking example of such a strategy [43].

However, it is not uncommon for there to be a mismatch between the patient's perception and the clinician's assessment [39]. For example, in some instances the patient's perception of CHF and disease severity has also been overestimated when compared to physician's clinical findings [44]. This incongruence may be due to the validity of tools used to assess patient perception or, an underestimation by clinicians of patient's with HF. Therefore valid and reliable PROs can be an important communication tool. These measures provide a useful way to gather and communicate evidence about treatment risks and benefits. This information can be used to highlight particular treatment benefits or to provide a way to differentiate the patient benefits among competing treatments with similar clinical efficacy [45]. This will assist clinicians in providing patients with better information about potential effects of treatment, and thus lead to better treatment decisions. Data derived from PROs can also enable patients to increase their understanding about their illness and treatment risks and benefits. This is also a potentially useful strategy in increasing individuals' participation in their own treatment and in health care decision making. Patient adherence is a major impediment to the effectiveness of therapies. Increased patient satisfaction with a treatment has been shown to be related to adherence [9]. Accordingly, evaluating satisfaction with treatment may assist health care providers in understanding the issues influencing treatment adherence and may help identify aspects of the management plan that require improvement to enhance long-term treatment outcome [46]. The Innovative Care for Chronic Conditions (ICCC) framework (Fig. 1) describes the importance of community and policy aspects of improving health care for chronic conditions [47]. This model highlights the importance of considering discrete yet linked attributes at the *micro*-(patient and family), *meso*- (health care organisation and community), and *macro*-(policy) levels, underscoring the need for a multifaceted approach to health care outcome assessment. To date, a comprehensive model for health service evaluation including all these critical elements has not been tested.

3. Discussion

Patient assessments are important elements of the evaluation of treatment impact, alongside other clinical indicators. Bioethics has emphasized the importance of the patient's point of view in health care decisions through its call to respect patient autonomy. Outcome research has specified the importance of the patient's perspective on the goal of medical care in its bid to accentuate patient-centred outcome such as quality of life [39]. It is recognised that linking patient-reported health with physiological markers of disease provide not just unique information in patient care, but also help to determine the severity of disease and monitor the trajectory of illness [33]. These factors are also important in informing cogent policy decisions.

It is hard to dispute that the science of PROs is advanced, as illustrated in the vast numbers of psychometric instruments available to assess these items. Perhaps what remains is the greatest challenge is moving assessment of these constructs beyond the research setting to routine clinical practice, administrative data sets and in contexts that will inform clinical and policy makers. The relevance of the applicability of clinical trial evidence to real world populations is commonly questioned [48]. Often participants in clinical trials are commonly younger, have less comorbid conditions and commonly do not have the challenges of poor health literacy and cognitive impairment that impact on outcomes of HF [49]. This conundrum is illustrated in the adverse events related to pharmacotherapy when agents move from the clinical trial to the usual care setting.

Registry data provides a useful insight into real world situations that can provide policy makers with reliable and valid data to inform policy decisions. A number of registries have provided useful data to inform HF management in the real world setting [50–53]. Many of these registries provide useful data – particularly relating to how factors such as socioeconomic determinants, level of insurance, and ethnicity impact on health-related outcomes [54]. Data for these registries is often collected from administrative data sets that do not routinely use patient-reported outcomes. Including valid and reliable PROs in these data sets may be useful in health service planning

As shown in the Innovative Care for Chronic Conditions Framework in Fig. 1, a Positive Policy Framework is contingent upon understanding the needs of patients and their families. This can be achieved through a range of means, such as community consultations, representations of democratically elected candidates and lobbying from particular consumer organisations. A potentially more equitable, just, reliable and valid mechanism would be to include PROs in routine clinical assessments, clinical trials and registries to allow an informed decision on how conditions, treatment and health care interventions impact on the lives of individuals and their families. For example, in Australia, the most rapidly increasing population are centenarians – many of whom will endure and die of HF. Yet, we know little of their needs and service planning requirements [55]. Further, the development of reliable and valid metrics that allow for the integration of micro-, meso- and macro-elements of health service delivery are needed. Health care policy, often constrained by partisan politics and influence of powerful lobby groups, can struggle to keep pace with the strategies needed to administer and monitor the increasing expense and complexity of health care [56]. In HF, the development of innovative treatments, such as implantable cardiac defibrillators, left-ventricular assist devices have outpaced the debate and discussion of the applicability and relevance to particular groups [57,43]. Despite benefits some patients may derive from these medical interventions, the default plan of providing these devices or procedures regardless of patient's wishes and priorities need to be reconsidered by policy makers. Furthermore, their use entails substantial financial, physiological, and psychological costs to patients, health care system and community in general. Policy makers and clinicians alike need to allocate limited resources to patients

with HF to serve their interests and perspectives. Understanding the impact of these interventions on individuals is likely to be critical in the future and require extensive debate and discussion.

4. Conclusions

Health care policy needs to be concerned with the financing of health care systems, access to and the outcomes of the quality of care. Contingent in this assessment is how health care services and treatments impact on the individual and their families. This article has used HF as an exemplar of a chronic condition that is costly, deadly and burdensome to individuals and communities. We need to consider the impact of CHF on the individual to inform health care policy. As the burden of chronic conditions grow and the population ages, we need to develop and refine the metrics of including the perspectives of patients on both an individual and population level to effectively evaluate the efficacy of health care intervention, treatment and planning. This in turn will lead policy makers to make decisions about service supply and health care spending that reflects the balance of extending life with improved quality. Health span or life span will become the issues that will be critical to address for both clinicians and policy makers alike.

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