THE IMPACT OF TELEMEDICINE IN THE
REHABILITATION OF PATIENTS WITH
HEART DISEASES

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ABSTRACT

The potential that telemedicine interventions may have in effectively delivering remote specialized cardiovascular care to large numbers of patients with heart diseases has recently come under question. In the first phase of this thesis, a systematic review and meta-analysis was conducted to compare the impact of a basic form of telemedicine that is regular patient follow-up by telephone, with usual care for individuals with coronary artery disease following their discharge. In the second phase of this thesis, a network meta-analysis, using Bayesian methods for multiple treatment comparisons, was conducted to compare the more complex forms of telemedicine for patients with heart failure. In the third and final phase of this thesis, a randomized controlled trial was designed to compare the impact of two forms of telemedicine, identified in the earlier two phases as being the most promising, on clinical outcomes, cardiac risk factors and patient reported outcomes.
EXECUTIVE SUMMARY

Cardiac rehabilitation programs have been previously shown to improve patient outcomes and reduce the likelihood of further cardiac illness through strategies that target risk factors for cardiovascular disease. Despite their benefits however, patient participation and adherence to these programs remains suboptimal. At the same time, the provision of high quality care to an expanding population of individuals with chronic heart diseases is becoming increasingly difficult.

Interventions like telemedicine have therefore been considered as a potential means to deliver remote specialist cardiovascular care to individuals who require regular monitoring and follow-up. Unfortunately, the evidence regarding the effectiveness of these interventions has been highly variable. The inconsistency of this evidence stems from relying on several small and underpowered studies as well as systematic reviews that have adopted very broad definitions of telemedicine. As a result, previous studies have been inconsistent in their conclusions regarding telemedicine and systematic reviews have examined multifaceted interventions, which made it difficult to determine specifically which form of telemedicine appears most effective.

As part of the thesis, three manuscripts were prepared. In the first manuscript, a systematic review and meta-analysis that focused on evaluating the impact of a single form of telemedicine was conducted. The objective of this review was to compare the impact of structured telephone follow-up with usual care after discharge with regards to: 1) clinical
events (death and hospitalization); 2) cardiac risk factors (smoking cessation, medication adherence, systolic blood pressure and low-density lipoprotein levels); and patient reported outcomes (quality of life, depression and anxiety). Findings from this review determined that a basic form of telemedicine can be beneficial for individuals who have moderate coronary artery diseases by reducing all-cause hospitalizations, controlling systolic blood pressure, aiding smoking cessation and reducing feelings of depression and anxiety.

The second manuscript resulted from conducting a network meta-analysis for heart failure patients that compared across usual care and the following five forms of telemedicine: 1) structured telephone support; 2) telemonitoring; 3) structured telephone support and telemonitoring delivered together; 4) video monitoring; and 5) electrocardiographic data monitoring. This analysis identified telemonitoring and structured telephone support as the interventions considered most effective in reducing the outcome of death and hospitalization due to heart failure. The use of Bayesian methods for multiple treatment comparisons allowed for the use of all available data from direct and indirect comparisons to achieve more robust and precise estimates. It also allowed for the inference of intervention comparisons that have not yet been made in the literature.

Based on the findings from the aforementioned manuscripts, a randomized controlled trial was designed for the third manuscript. This trial will compare the effectiveness of structured telephone support and telemonitoring with telemonitoring alone for Heart Failure patients. The importance of this study stems from the lack of adequately powered individual studies that compare one active form of telemedicine to another as opposed to
usual care which has been the typical comparison of choice in previous studies. A cost utility analysis comparing both aforementioned forms of telemedicine will also be conducted as part of the analyses for this randomized controlled trial.

Findings from this thesis have identified the current inconsistency in the evidence around the use of telemedicine in cardiac rehabilitation. This work also highlights the lack of evidence that compares telemedicine interventions against each other and not only to standard care. Using a novel Bayesian approach all currently available data were used and this resulted in better understanding effectiveness of five forms of telemedicine as they compare to one another as well as usual care post-discharge.

The recommendations from this thesis can be summarized as follows:

1. There is a need for a unified classification of these various forms of telemedicine to serve as guidance for further more specifically defined systematic reviews and meta-analysis on telemedicine in heart diseases.
2. A clinician’s decision regarding whether or not to incorporate telemedicine into his/her patient care should be based on each individual patient’s specific rehabilitation goals.
3. Larger randomized controlled trials that compare one form of telemedicine to another with longer follow-up lengths and safeguards to protect against the inability to blind the individuals receiving these interventions are needed.
CONTRIBUTION OF THE AUTHORS

Three manuscripts have been prepared for publication as part of this thesis. All manuscripts are co-authored by the student (AK) and his supervisor, Dr. George A. Wells. The student is the first author of all papers, having been primarily responsible for the conception of the study, data collection, analysis, and the writing of the manuscripts. Dr. Wells provided all the guidance needed throughout the process.
ACKNOWLEDGEMENTS

A great poet once said, “Without my family, all I am left with is a shadow of me.” So above all else, I want to thank my parents Alaa Kotb and Zahira El Sayed, my brother, Mohamed Kotb and my wife, Zuzanna Kucharski for their unconditional love and support. If it was not for the sacrifices they have all made for me, I would not be where I am right now. They give me the strength to keep moving forward and the inspiration to continue to pursue my dreams no matter what happens.

I also want to thank Dr. George A. Wells for all the guidance and support that he has given me. I met Dr. Wells the first day of orientation for the Master of Science in Epidemiology program at the University of Ottawa and I wanted more than anything for him to accept me as his graduate student. I want to thank him for believing in me. He has inspired me and I feel absolutely honored and privileged to have learned so much from him.

Finally, I would like to thank someone who has been like a brother to me, Mohammed Rashid. Whether we were volunteering in Tanzania, applying to medical schools, or becoming league champions with the Westboro Wolves Soccer Club, Rashid was always there. He is the younger brother I never had, the most talented number 10 I have ever played alongside and the best friend I have always needed. One day he will have his own thesis to submit and acknowledge me in but for now, I want to thank him and let it be known that this thesis would not have been the same without his support.
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<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ACS</td>
<td>Acute Coronary Syndrome</td>
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<tr>
<td>AMI</td>
<td>Acute Myocardial Infarction</td>
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<tr>
<td>CABG</td>
<td>Coronary Artery Bypass Graft</td>
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<tr>
<td>CAD</td>
<td>Coronary Artery Disease</td>
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<tr>
<td>CADTH</td>
<td>Canadian Agency for Drugs and Technologies in Health</td>
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<tr>
<td>CHD</td>
<td>Coronary Heart Disease</td>
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<tr>
<td>CHF</td>
<td>Chronic Heart Failure</td>
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<tr>
<td>CI</td>
<td>Confidence Interval</td>
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<tr>
<td>CIHR</td>
<td>Canadian Institute of Health Research</td>
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<tr>
<td>CR</td>
<td>Cardiac Rehabilitation</td>
</tr>
<tr>
<td>CrI</td>
<td>Credible Interval</td>
</tr>
<tr>
<td>CVD</td>
<td>Cardiovascular Diseases</td>
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<tr>
<td>DIC</td>
<td>Deviance Information Criterion</td>
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<tr>
<td>DSMB</td>
<td>Drug Safety Monitoring Board</td>
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<tr>
<td>HF</td>
<td>Heart Failure</td>
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<tr>
<td>IRB</td>
<td>Institutional Review Board</td>
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<tr>
<td>IVR</td>
<td>Interactive Voice Response</td>
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<tr>
<td>LDL</td>
<td>Low-Density Lipoprotein</td>
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<tr>
<td>MA</td>
<td>Meta-Analysis</td>
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<tr>
<td>MCS</td>
<td>Mental Composite Score</td>
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<tr>
<td>MI</td>
<td>Myocardial Infarction</td>
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<tr>
<td>NMA</td>
<td>Network Meta-Analysis</td>
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<tr>
<td>Acronym</td>
<td>Description</td>
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<tr>
<td>NYHA</td>
<td>New York Heart Association</td>
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<tr>
<td>OR</td>
<td>Odds Ratio</td>
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<tr>
<td>PCI</td>
<td>Percutaneous Coronary Intervention</td>
</tr>
<tr>
<td>PCS</td>
<td>Physical Composite Score</td>
</tr>
<tr>
<td>PI</td>
<td>Primary Investigator</td>
</tr>
<tr>
<td>PTCA</td>
<td>Percutaneous Transluminal Coronary Angioplasty</td>
</tr>
<tr>
<td>QOL</td>
<td>Quality of Life</td>
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<tr>
<td>RCT</td>
<td>Randomized Controlled Trial</td>
</tr>
<tr>
<td>RPM</td>
<td>Remote Patient Monitoring (Telemonitoring with Structured Telephone Support)</td>
</tr>
<tr>
<td>RR</td>
<td>Relative Risk</td>
</tr>
<tr>
<td>SAB</td>
<td>Scientific Advisory Board</td>
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<tr>
<td>SBP</td>
<td>Systolic Blood Pressure</td>
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<tr>
<td>SMD</td>
<td>Standardized Mean Difference</td>
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<tr>
<td>SR</td>
<td>Systematic Review</td>
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<td>STS</td>
<td>Structured Telephone Support</td>
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<tr>
<td>TM</td>
<td>Telemonitoring</td>
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<tr>
<td>UC</td>
<td>Usual Care</td>
</tr>
<tr>
<td>UOHI</td>
<td>University of Ottawa Heart Institute</td>
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<td>WHO</td>
<td>World Health Organization</td>
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CHAPTER ONE: INTRODUCTION

1.1 Rationale

Cardiovascular disease (CVD) is the leading cause of death worldwide. The World Health Organization (WHO) estimated that 17.5 million people died from CVD in 2005. At the time, this represented approximately 30% of the world’s mortality. In the past decade, the prevalence of CVD increased by 18.2%. In order to reduce the burden caused by CVD, effective primary and secondary prevention of these diseases is crucial.

Cardiac rehabilitation (CR) is offered to individuals after cardiac events to aid recovery and reduce the likelihood of further cardiac illness. CR programs have been previously shown to improve physical health as well as decrease subsequent morbidity and mortality through exercise, education, behavior change, counseling and other strategies aimed at targeting traditional risk factors for cardiovascular disease. Despite these benefits however, patient participation in CR programs remains suboptimal. Some of the main reasons people give for not taking part in cardiac rehabilitation are difficulties in regularly attending sessions and reluctance to take part in group-based classes.

Patient adherence to rehabilitation is an additional concern. It is estimated that between 40% and 60% of people do not take medication as prescribed because of forgetfulness, changing medication schedules or busy lifestyles. Medications unused and/or returned to pharmacists are estimated to cost £100 million per annum in the United Kingdom. In the
United States, the annual cost of illness due to non-adherence has been reckoned at US $100 billion.¹⁵

To improve adherence, Osterberg identified the following four approaches: patient education; improved dosing schedules; increased access to health care; and improved communication between physicians and patients.¹⁶ Some evidence suggests as well that interventions involving motivational communications delivered through letters, telephone calls and home visits may be effective in increasing the uptake of cardiac rehabilitation.¹⁷ This offers promise as the provision of high quality care to a rapidly expanding population of older patients with chronic heart conditions becomes increasingly difficult. Specialist cardiovascular clinics are available only to a minority of patients and do not have the capacity for frequent patient review. On the other hand, patients may be unwilling or unable to make frequent clinic attendance due to financial, transport or disability constraints.¹⁸

As a result, many studies have recently sought to examine whether or not interventions that aim to facilitate the provision of remote specialized care to a large number of patients who may otherwise have limited access to healthcare services could be effective and in which patient populations would they be most beneficial. These interventions are commonly known as “Telemedicine”.

1.2 Outline and objectives

This thesis has been formatted as a manuscript-based thesis. Three manuscripts have been prepared, in addition to a background chapter (Chapter 2) and a discussion and recommendations chapter (Chapter 6).
The following is an overview of the objectives of each chapter.

Chapter One

This introductory chapter provides an overview of the organization of the thesis and the objectives of each chapter.

Chapter Two

This chapter provides the rationale for the thesis. It presents the necessary background information and the current evidence around the application of telemedicine during cardiac rehabilitation.

Chapter Three

This is a manuscript based on the results of a systematic review and meta-analysis to determine the effectiveness of structured telephone support in the treatment and management of individuals with coronary artery diseases (CAD). The objective of this analysis was to compare the impact of structured telephone support interventions, delivered during cardiac rehabilitation, on clinical events, cardiac risk factors and patient reported outcomes in individuals with CAD compared to receiving usual follow-up care alone.
**Chapter Four**

This is a manuscript based on the results of a network meta-analysis of multiple telemedicine interventions for individuals with heart failure (HF). The objective of this analysis was to examine the impact of these different forms of telemedicine interventions on the outcomes of death, all-cause hospitalization and heart failure hospitalization in heart failure patients.

**Chapter Five**

This is a manuscript based on the protocol for a randomized controlled single-blinded intervention trial. The objective of this manuscript was to design a study that will compare the two forms of telemedicine identified as most effective and compare them against each other and a newly designed intervention for coronary artery diseases (CAD) patients with and without heart failure.

**Chapter Six**

This chapter brings together the results of the systematic review and meta-analysis, network meta-analysis, and the design of a randomized controlled trial.
1.3 References


CHAPTER TWO: BACKGROUND

2.1 Telemedicine in individuals with heart failure

To date, most of the evidence available has been focused on examining the effect of telemedicine on individuals with Heart Failure (HF). HF is a complex debilitating syndrome that results from a cardiac dysfunction that impairs the ability of the ventricle to fill with or eject blood.\(^1\) Given the substantial burden HF exerts on healthcare systems, because of the high consumption of human resources due primarily to repeated and lengthy admissions to hospital, it is not surprising that various interventions have been designed and examined for this population.\(^2\) Despite the abundance in evidence, the conclusions being drawn across studies have been inconsistent.

Telemonitoring is a form of telemedicine that typically involves the transmission of information on symptoms and signs between a healthcare professional and the patient. Earlier systematic reviews such as those by Louis in 2003 and Chaudhry in 2007 concluded that telemonitoring might have an important role in the delivery of health care for patients with heart failure but that the evidence was still limited.\(^3,4\) In 2007, a systematic review and meta-analysis of randomized controlled trials found that remote monitoring programs for patients with heart failure reduced HF-related admissions to hospital and all-cause mortality by nearly one fifth while improving health related quality of life, but had no significant effect on all cause admission to hospital.\(^5\) Similarly, in 2010 a systematic review by the Canadian Agency for Drugs and Technologies in Health (CADTH), found that home telemonitoring of heart failure patients reduced mortality and hospitalizations compared to usual care. Additionally, they found that
In 2011, a systematic review and meta-analysis of randomized controlled trials comparing telemonitoring to usual care found that telemonitoring reduced all-cause mortality and hospital admissions resulting from heart failure but had no effect on overall hospital admissions, length of stay, medication adherence or cost. The general conclusion however, was that telemonitoring alone was insufficient to reduce readmission rates and improve quality of life, and must be integrated with nurse visits and specialist follow-up. As the benefit of telemedicine seemed to be consistently proven, studies began to examine whether these systems were cost-effective. A systematic review comparing the cost of telemonitoring and usual care concluded that although heart failure telemonitoring would require an initial financial investment, it would substantially reduce costs in the long term particularly by reducing re-hospitalization and travel costs.

Despite these promising findings however, it is important to note that the aforementioned reviews have all examined very diverse telemedicine interventions. Not only did the interventions differ in their intensity, duration and frequency of administration from one review to the next but also within the included studies of each review. The comparator was, in most cases, considered “standard” or “usual” care however, this definition also varied significantly between studies. These clinical differences could lead to difficulties in combining and comparing results. Several reviews included trials that tested multifaceted approaches (multidisciplinary input, home/clinic visits, telephone support). As a consequence, it has been difficult to identify the benefits of the unique components of each intervention.
This became the focus of a recent Cochrane review. In this review, Inglis and colleagues included trials examining the impact of standard telephone or more advanced telemonitoring technology systems (e.g. electronic transfer of physiological data – electrocardiograph (ECG), blood pressure (BP), weight, pulse oximetry, respiratory rate and medicine administration) if they were delivered to patients with HF living in the community as the only aftercare intervention, without home visits or intensified clinic follow-up. The aforementioned interventions were found to reduce the rate of death from any cause by 44% and the rate of heart-failure-related hospitalizations by 21%.

Once again, these results were later challenged by a large multi-center randomized controlled trial of heart failure patients. The study by Chaudhry and colleagues found no reduction in the risk of readmission or death from any cause with telemonitoring as compared with usual care. There were also no reductions in the risk of hospitalization for heart failure, the number of days in the hospital, or the time to readmission or death. Moreover, subgroup analyses failed to identify a group for which the intervention was effective.

To conclude, even though there has been a substantial amount of literature supporting the use of various telemedicine for HF patients, there continues to be a need for more consistent results given the contradictory conclusions that have emerged in more recent evidence. Most reviews have included participants with symptomatic heart failure, but the definition and inclusion criteria differed amongst the studies, with some studies reporting few details of the diagnostic criteria for heart failure. Also, reviews have often included studies that varied considerably in the type telemedicine services offered, sample sizes and follow-up durations. To
determine which interventions are effective and the particular subset of HF patients that experienced the greatest treatment benefit, we will conduct a network meta-analysis.

2.2 Telemedicine in individuals without heart failure

More recently telemedicine interventions were examined for their use in patients with less advanced Coronary Artery Diseases (CAD). CAD results from an impedance or blockage of one or more arteries that supply blood to the heart. This in turn, produces symptoms and signs of CAD that can include chest pain (angina pectoris), heart attack (myocardial infarction), and/or sudden death. Compared to HF patients however, far less is known about the potential impact of telemedicine interventions on CAD-related outcomes.

It was not until 2009 when Neubeck and colleagues systematically reviewed and presented the first and only quantitative assessment of telemedicine interventions for secondary prevention of CAD. The results showed a non-significant reduction in all-cause mortality with participation in telemedicine compared with usual care. However, the results also showed significantly favorable changes in total cholesterol, lipoprotein levels, and smoking with telemedicine participation compared with usual care at longer follow-up. The aforementioned are important cardiac risk factors for reducing the likelihood of recurrent CAD morbidity and/or mortality.

Neubeck’s findings are somewhat consistent with those for heart failure patients where telemedicine interventions have not been found to reduce the risk of death. However this review was limited by the lack of blinding of outcome attainment to group allocation. Most importantly, it included trials that varied with regards to the telemedicine intervention used. Each intervention was somewhat different in its characteristics and targets. While most
interventions used telephone-guided care, some also used the internet and others included weekly and monthly sessions initiated and led by nurses or pharmacists.

When multifaceted interventions are examined, it becomes difficult to determine specifically which method of telemedicine appears most effective for this particular patient population. We will therefore conduct the first systematic review and meta-analysis to examine specifically the effects of regular structured telephone support systems on Coronary Artery Disease (CAD) patients’ outcomes. These systems involve contact between patients and their healthcare providers that do not necessarily incorporate the transmission of physiological data.

These systems contact patients at home, early in their recovery phase, to ask a sequence of questions that screen for problems such as inadequate weight control or shortness of breath. Patients receive calls at scheduled times following their discharge and their responses are electronically recorded in a database where clinicians can view them. As a result, they may lead to prompt interventions in the recovery period after discharge which may improve risk factor modification as well as potentially reduce hospital readmissions and mortality.
2.3 References


9. Inglis SC, Clark RA, McAlister FA, Ball J, Lewinter C, Cullington D, Stewart S, Cleland JGF.
   Structured telephone support or telemonitoring programmes for patients with chronic
   CD007228. DOI: 10.1002/14651858.CD007228.pub2.

    England Journal of Medicine, 2301-2309


    prevention of coronary heart disease: a systematic review. European Journal of
CHAPTER THREE: A SYSTEMATIC REVIEW AND META-ANALYSIS

The following is a manuscript prepared for publication, based on a systematic review and meta-analysis that compared the impact of structured telephone support interventions on clinical events, cardiac risk factors and patient reported outcomes with usual care in individuals with coronary artery diseases. The objective of this review was to determine if a basic form of telemedicine could be more effective in achieving better patient outcomes than standard post-discharge care in the period of cardiac rehabilitation.

A copy of The Cochrane Collaboration’s tool used to assess the risk of bias in included studies is provided in Appendix A of the thesis.

A copy of The SIGN-50 Checklist used to assess the methodological quality of the included studies is provided in Appendix B of the thesis.

This manuscript was co-authored by the student (AK), his supervisor, Dr. George A. Wells and Dr. Shu-Ching Hsieh. The student is first author of this paper, having been primarily responsible for the conception of the study, data collection, analysis and the writing of the manuscript. Dr. Wells provided guidance and valuable feedback throughout the process and Dr. Hsieh was integral for the stages of study selection and data extraction.
The Effect of Telephone Support Interventions on Coronary Artery Disease (CAD) Patient Outcomes during Cardiac Rehabilitation: A systematic review and meta-analysis.

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Total word count: 3,567 words (text only)

This manuscript includes one (1) table, three (3) figures, and four (4) appendices.
Abstract

Background: Cardiac rehabilitation is offered to individuals after cardiac events to aid recovery and reduce the likelihood of further cardiac illness. However, patient participation remains suboptimal and the provision of high quality care to an expanding population of patients with chronic heart conditions is becoming increasingly difficult. As a result, the feasibility and effectiveness of using telemedicine interventions to deliver care have recently been considered. A systematic review and meta-analysis was conducted to determine the effect of telephone support interventions compared with standard post-discharge care on coronary artery disease patient outcomes.

Methods: The Cochrane Library, MEDLINE, EMBASE, and CINAHL were searched. Reference lists of included studies were also checked. Randomized controlled trials that directly compared telephone interventions with standard post-discharge care in adults following a myocardial infarction, angina or a revascularization procedure were included. Study selection and data extraction were carried out independently by two reviewers. Where appropriate, outcome data were combined and analyzed using a random effects model. For dichotomous variables, odds ratios (OR) and 95% confidence intervals (CI) were derived for each outcome. For continuous variables, standardized mean differences (SMD) and 95% CI were calculated for each outcome.

Results: Twenty-six studies met the inclusion criteria. No difference was observed in mortality between the telephone group and the group receiving standard care (OR 1.12 [0.71, 1.77]). The intervention was significantly associated with fewer hospitalizations than the comparison group (OR 0.62 [0.40, 0.97]). Significantly more participants in the telephone group stopped smoking (OR 1.32 [1.07, 1.62]); had lower systolic blood pressure (SMD -0.22 [-0.40, -0.04]); lower
depression scores (-0.10 [-0.21, -0.00]); and lower anxiety scores (-0.14 [-0.24, -0.04]). However, no significant differences were observed for medication adherence (OR 0.93 [0.73, 1.20]); low-density lipoprotein levels (SMD -0.10 [-0.23, 0.03]); physical composite scores (SMD 0.12 [-0.03, 0.28]); and the mental composite score for quality of life (SMD 0.01 [-0.23, 0.26]).

**Conclusions:** Regular telephone support interventions may help increase the uptake of secondary prevention activities and reduce further hospitalization.
Introduction

Cardiac rehabilitation (CR) is offered to individuals after cardiac events to aid recovery and reduce the likelihood of further cardiac illness. They have been previously shown to improve physical health as well as decrease subsequent morbidity and mortality through exercise, education, behavior change, counseling and other strategies aimed at targeting traditional risk factors for cardiovascular disease. Despite these benefits however, patient participation in these programs remains suboptimal.

Some evidence suggests that interventions involving motivational communications delivered through letters, telephone calls and home visits may increase the uptake of cardiac rehabilitation. This offers promise as the provision of high quality care to an expanding population of older patients with chronic heart conditions becomes increasingly difficult. On the other hand, patients may be unwilling or unable to make frequent clinic attendance due to financial, transport or disability constraints.

To be delivered alongside standard post-discharge rehabilitative care, interventions commonly referred to as “Telemedicine” involve the use of telecommunication to provide clinical health care at a distance are being considered. To date, much of the evidence available has been focused on examining the effect of complex and multifactorial telemedicine interventions for heart failure (HF) patients. HF is a complex debilitating syndrome that results from a cardiac dysfunction that impairs the ability of the ventricle to fill with or eject blood. More recently however, more basic telephone support interventions have been adapted for use in coronary artery disease (CAD) patient populations. CAD is one of the most common forms of heart
disease that results from an impedance or blockage of one or more arteries that supply blood to the heart.  

Previous reports have examined the impact of multifaceted interventions on chronic diseases in general. When multifaceted interventions are examined, it becomes difficult to determine specifically which method of telemedicine appears most effective for this particular patient population. The aim of this systematic review and meta-analysis is to examine the literature on the impact of receiving structured telephone support, during cardiac rehabilitation, on clinical events, cardiac risk factors and patient reported outcomes in individuals with CAD compared to receiving usual follow-up care alone. The research questions addressed were: (1) What impact does structured telephone support (STS) have on mortality and hospitalization? (2) What impact does STS have on controlling risk factors such as smoking, systolic blood pressure, and low-density lipoprotein as well as adherence to medication? (3) What does STS have on patient reported outcomes such as quality of life, anxiety and depression?

**Methods**

*Search methods for identification of studies:* Relevant randomized controlled trials published before September 2012 were identified by searching the following databases: Cochrane Central Register of Controlled Trials (CENTRAL), Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment Database (HTA) on The Cochrane Library, MEDLINE, EMBASE, CINAHL, AMED, and the Web of Knowledge. Language restrictions were not applied to any of the searches. Bibliographies of included trials were examined to identify other potentially relevant studies. The search strategies are described in Appendix 1.
Criteria for considering studies: Randomized controlled trials were included if they directly compared the impact of telephone-delivered post-discharge interventions with standard care at discharge in adults (18 years or older) who had experienced a myocardial infarction (MI), a revascularization procedure (coronary artery bypass grafting (CABG) or percutaneous transluminal coronary angioplasty (PTCA)), and those with angina, or angiographically defined coronary heart disease. Primary outcomes included all-cause mortality and hospitalizations. Secondary outcomes included depression, anxiety and quality of life as well as measures taken to reduce the risk of further cardiac illness such as smoking cessation, reducing systolic blood pressure, cholesterol levels and increasing adherence to medication.

Selection of studies: In the first phase of screening, the titles and abstracts of all identified citations were screened by two independent reviewers (AK and SC). In the second phase of screening, full manuscripts were retrieved and screened by two independent reviewers on the basis of our predefined patient population, intervention, comparison, outcomes and study design of interest. Disagreements were resolved through discussion or through adjudication by a third reviewer (GW).

Data extraction: For each included paper, one review author (AK) extracted data and a second author (SC) checked the extracted data and disagreements were resolved by discussion between the two review authors. If no agreement could be reached, a third author (GW) was required for adjudication.

Assessment of risk of bias in included studies: The SIGN-50 checklist and the Cochrane Collaboration's tool for assessing risk of bias (ROB) were used to evaluate the methodological
quality of included trials. Two independent reviewers conducted the quality assessments (AK and SC). Disagreements between reviewers were resolved by discussion or through adjudication by a third reviewer (GW).

**Data synthesis:** The primary analysis was a comparison of telephone follow-up with usual care. Heterogeneity amongst included studies was explored qualitatively by comparing the characteristics of included studies and quantitatively using Cochrane’s Q test and I² statistic. For continuous data (using the same measuring instrument) the weighted mean difference (WMD) and 95% confidence intervals (CI) are reported. Where the studies have used different instruments to measure the same conceptual outcome, the standardized mean difference (SMD) is reported. In studies that report dichotomous data, the odds ratios (OR) and confidence intervals (CI) are reported. To account for heterogeneity and take a more conservative approach, the analyses were carried out using the random-effects model are presented. To ensure that studies included in the analysis were appropriately weighed in the random effects models, analyses using fixed effect models were conducted for comparison. No difference between the models is expected where no substantial heterogeneity is observed.

**Results**

**Search results:** The electronic search conducted yielded a total of 1,538 titles. The reference lists of studies later included were hand-searched and resulted in the selection of 53 studies for additional screening. After duplicates were removed, the titles and abstracts of 1,235 studies were screened. A total of 1,075 studies were excluded and 160 studies were retrieved for possible inclusion. After examining their full texts, 26 studies were included and 134 were
excluded. The study selection process and the reasons for exclusion are summarized in the PRISMA flow diagram shown in Figure 1.

Description of studies: All included randomized controlled trials (4,081 participants) compared a telephone intervention designed to improve cardiac patients’ outcomes directly to standard post-discharge care. Of the 26 included papers, 13 studies had longer than 6 months of follow-up. Seven studies reported less than 6 months of follow-up and 6 reported outcomes at 6 months. Sample sizes varied considerably across studies (range: 59 to 792) as well as the number of calls made to participants (range: 3 to 24). Typically, the telephone support intervention was delivered by a nurse but in some instances, the calls were made by various other professionals such as exercise specialists, educators, dietitian, pharmacy specialists, study coordinators, physicians or a peer volunteer. Characteristics of all included studies are summarized in Table 1. A more detailed description of included studies is available in Appendix 2.

Risk of bias in included studies: Using the SIGN-50 quality assessment tool for randomized controlled trials, 14 studies were considered to be of high quality, 11 were considered to be of acceptable quality and 1 was considered to be low (see Table 1). A summary of the risk of bias of included studies is described in Figure 2. The risk of bias assessment of each study is detailed in Appendix 3.

Structured telephone support interventions versus usual care

Figure 3 provides a summary of the intervention’s main effects compared to usual care for the following outcomes of interest: death, hospitalization, smoking cessation, medication
adherence, systolic blood pressure, low-density lipoprotein levels, quality of life, depression and anxiety. Detailed reporting of the meta-analysis of each of the aforementioned outcomes is available in Appendix 4.

**Clinical events:** Data on all-cause mortality was available and considered appropriate to be combined across 11 studies. The overall effect estimate found showed no difference in the odds of mortality between the intervention and comparison group [OR 1.12 95% CI (0.71, 1.77)] (Figure 3). Despite showing no statistical heterogeneity ($I^2 = 0\%$) however, we further examined the studies according to their patient population, intervention, comparison and outcomes of interest.

A series of sensitivity analyses were conducted, first by excluding the studies by McLaughlin (2005) and Reid (2007). For the study by McLaughlin (2005) patients were selected on the basis of showing depressive or anxiety symptoms,$^{23}$ and in the study by Reid (2007) they were required to all be smokers.$^{30}$ The overall effect however remained non-significant [OR 1.19 95% CI (0.75, 1.89)]. Despite not showing statistical significance, the odds of death were lower for the telephone group [OR 1.07 95% CI (0.64, 1.78)] where the usual discharge care involved the provision of information about CAD and risk reduction, than when patients received standard physician follow-up [OR 1.37 95% CI (0.51, 3.66)]. Finally, studies were examined according to the duration of their treatment and follow-up periods. Studies of 6 months or less duration were considered short-term while studies as long as 12 months were considered medium-term and studies longer than 12 months as long-term. At 6 months or less, the overall effect was indicative of a lower odds of death for the intervention group than the comparison [OR 0.76
95% CI (0.22, 2.68)]. The overall effect estimate approached 1 indicating approximately no
difference between the groups when we considered medium-term studies [OR 0.88 95% CI
(0.40, 1.93)]. Interestingly also, the overall effect estimate was greater than 1 when longer term
studies were analyzed [OR 1.30 95% CI (0.70, 2.43)]. Despite these findings not showing
statistical significance, there appears to be fewer deaths in the telephone intervention group
than the comparison when the intervention is first introduced but eventually this reduction is
reversed. This may be suggestive of a detrimental effect of withdrawing the telephone
intervention from patients who relied on it to reach their rehabilitation goals.

A total of 4 studies reported on hospitalization after discharge. Heterogeneity was further
examined according to the PICO statement of individual trials. The statistical measure of
heterogeneity was reduced ($I^2=15\%$) and the overall effect estimate indicated significantly
lower odds of hospitalization [OR 0.62 95% CI (0.40, 0.97)] in the telephone group. It is
important to note however, that when a sensitivity analysis was conducted with and without
the most outlying study, Beckie (1989), the significant effect was no longer found [OR 0.68 95%
CI (0.45, 1.01)].

**Modifiable risk factors:** A total of 6 studies reported data on smoking cessation. When
combined together the overall effect estimate indicated significantly greater odds of smoking
cessation in the group receiving the telephone intervention [OR 1.32 95% CI (1.07, 1.62)].

Two studies assessed patients' adherence to medication. The overall combined effect estimate
showed no significant difference between the two treatment groups [OR 0.93 95% CI (0.73,
1.20)].
A total of 4 studies reported data regarding the change in LDL levels between treatment groups. The overall combined standardized mean difference [SMD -0.19 95% CI (-0.39, 0.00)] was significant \((p = 0.05)\). This indicated that the telephone group had significantly lower LDL levels than the comparison group. The measure of statistical heterogeneity was considered substantially high \((I^2 = 58\%)\). Heterogeneity was examined according to the characteristics of included studies.

A sensitivity analysis was conducted where the most outlying study, Vale (2002), was excluded. Compared to the other 3 studies in this analysis, the study by Vale (2002) had the shortest follow-up and was the only study where usual care patients received educational material and the intervention was delivered by a dietitian who was primarily focused on lipid monitoring. Once excluded, the statistical measure of heterogeneity was reduced \((I^2 = 0\%)\) and the overall combined standardized mean difference was no longer significantly lower in the telephone group [SMD -0.10 95% CI (-0.23, 0.03)]. It is important to note, that the aforementioned study was the only one that showed a significant reduction in LDL levels in favor of the telephone group. This may be due to there being an immediate reduction in LDL levels at 6 months that does not persist in the longer term.

Two studies reported data on SBP differences between treatment groups. The overall calculated SMD was significantly lower for the telephone group [SMD -0.22 95% CI (-0.40, -0.04)].

**Patient reported outcomes:** In total, 3 studies measured and reported on quality of life. For the physical composite score (PCS) the overall calculated SMD was not significantly higher for the
intervention group [SMD 0.12 95% CI (-0.03, 0.28)]. Interestingly however, when studies were arranged according to the frequency of calls made, it appeared that the greater the number of calls made, the higher was the PCS for the intervention group.

For the mental composite score, there was no significance in the SMD between groups [SMD 0.01 95% CI (-0.23, 0.26)]. However there was relatively high degree of heterogeneity resulting from including the study by Smith. When excluded from the analysis, a reduction in the statistical measure of heterogeneity was observed ($I^2 = 0\%$) but there continued to be no significant difference found between groups.

In total 5 studies measured and reported on the outcome of depression. The overall calculated SMD showed a significantly lower ($p = 0.04$) depression score in the telephone group than the comparison [SMD -0.10 95% CI (-0.21, -0.00)]. The significance of this result did not change when studies by Gallagher (2003) were removed from the analysis. This analysis was considered since the study by Gallagher (2003) only included women and the study by McLaughlin (2005) only included patients who had shown some depressive or anxiety symptoms.

In total 6 studies reported data on anxiety. The overall calculated SMD indicated that participants in the telephone group had significantly lower anxiety scores than those in the comparison group [SMD -0.29 95% CI (-0.56, -0.01)]. However in examining the forest plot, study characteristics and $I^2$ value we found considerable heterogeneity. As a result we considered excluding the study by Beckie (1989). Compared to the remaining 5 studies, the study by Beckie (1989) had the shortest in follow-up lengths and included CAD patients who were less severe or acutely ill than CAD patients in other studies. Using a random effects model,
the overall calculated SMD demonstrated that the telephone group showed a trend towards lower anxiety scores than the comparison group [SMD -0.13 95% CI (-0.27, 0.00)] despite not being statistically significant (p = 0.06) Conversely, when a fixed effects model was examined the result was found to be significant [SMD -0.14 95% CI (-0.24, -0.04)].

To examine the effect of follow-up length we conducted a separate analysis to examine studies of 6 months of follow-up or longer. This analysis demonstrated that the participants in the telephone intervention group had significantly lower anxiety scores [SMD -0.18 95% CI (-0.30, -0.07)]. As a result, there appears to be a significant reduction in anxiety scores after 6 or more months of follow-up.

Since the study by Gallagher (2003) included women only, we conducted a sensitivity analysis according to sex and included only studies where the majority of participants were male. Once again participants in the telephone intervention group had significantly lower anxiety scores [SMD -0.18 95% CI (-0.30, -0.07)]. In the study by Gallagher (2003), no significant reduction was found for women in the telephone group compared to women in the comparison group (SMD 0.14 95% CI [-0.14, 0.42]).

Discussion

Many CAD patients continue to face challenges in maintaining adherence to recommendations for risk reduction such as compliance to medication, exercise, proper nutrition and smoking cessation. We hypothesized that the availability of remote monitoring and support services for recovering patients may facilitate access and improve patients’ participation in cardiac risk reduction programs. In this review, the majority of study participants were males aged
between of 50 and 70 years old. Outcomes considered included clinical events (all-cause mortality and hospitalization), modifiable risk factors (smoking cessation, medication adherence, low-density lipoprotein, and systolic blood pressure), and other patient outcomes (health-related quality of life, depression and anxiety). No evidence was found to support any additional benefit as a result of the telephone intervention in terms of a reduction in mortality, level of low-density lipoprotein or an improvement in patients’ quality of life scores and adherence to medications. Participants receiving the telephone intervention did however have significantly fewer hospitalizations. They also experienced significant reductions in systolic blood pressure and were more likely to stop smoking. Patients receiving the telephone intervention also had significantly lower depression and anxiety scores. Evidence from this systematic review and meta-analysis is therefore in support of the delivery of a regular telephone intervention alongside usual care for monitoring and supporting coronary artery disease patients following a cardiac event.

Similar to the reviews by Barth (2008) and by Neubeck (2009), telephone support was found to significantly promote smoking cessation in patients with coronary heart disease. Neubeck (2009) also demonstrated that participants in the telephone group had significantly lower systolic blood pressure (SMD -0.22 [-0.36, -0.07]). Our results were also consistent with findings from reviews by Neubeck (2009), Taylor (2010) and Whalley (2011) which found no strong evidence for reductions in total deaths. Whalley (2011) also found small or moderate improvements in depression. Finding from this review were consistent as the telephone group participants were also found to have significantly lower scores for depression and for anxiety.
Conversely however, the review by Taylor (2010) found no difference between groups in systolic blood pressure, total cholesterol, LDL-cholesterol or proportion of smokers at follow up or health-related quality of life. In their study however, there was no focus on telephone interventions but rather home-based monitoring. These interventions varied considerably across studies. Participants received interventions that ranged from home visits and devices such as ECG monitors to interventions like educational material in the form of self-help manuals and audiotapes.40

Given the nature of the intervention and the effect that this review sought to examine, it was neither feasible nor appropriate to blind participants and as such, some concern remains with regards to the risk of performance bias. With regards to publication bias, the potential risk was not examined for any outcome, with the exception of mortality, as a result of the low number of studies making it unreliable to examine funnel plots. This limitation must be taken into consideration given the fact that all studies included in this review were identified through electronic databases searching and the manual searching of bibliographies of included studies.

**Conclusion**

The effectiveness of this simple telephone intervention is of relevance given that most cardiac rehabilitation programs involve one or more of the following: routine monitoring, counseling, and educating. These aforementioned constituents can be feasibly delivered remotely using telephone technology as a medium. Since evidence from this review suggests that telephone support and monitoring appear more effective in reducing certain risk factors than others, physicians may identify, depending on each patient’s rehabilitation goals, which patients would
be most likely to benefit from the intervention. Through cardiac risk reduction and fewer hospitalizations, telephone support, may in turn help reduce the burden on the healthcare system while maintaining the delivery of specialist preventive care to patients who may otherwise not have access to them.

Acknowledgements

We gratefully acknowledge the help of Dr. Alaa Kotb for providing his expertise in the field of cardiology and Agnieszka Szczotka for her help in devising the search strategies needed for conducting this review.

Contributions of Authors

Under the supervision of Dr. George Wells, Ahmed Kotb conceived, designed and coordinated the review. Data collection for the review was performed by Ahmed Kotb and Shu-Ching Hsieh. Data management and analysis were performed by Ahmed Kotb and Dr. George Wells. Interpretation of the data was done by Ahmed Kotb, Shu-Ching Hsieh and Dr. George Wells. The review was written by Ahmed Kotb. General advice on the review was provided by Dr. George Wells and Shu-ching Hsieh.

Declaration of interest

None.
References


34. Stevens, B. (1985). The effectiveness of patient education follow-up by telephone on knowledge of post-myocardial infarction patients. (M.Nus., University of Alberta (Canada)). ProQuest Dissertations and Theses, . (303461144).


Tables and figures

Figure 1. Study flow diagram
<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Sample size</th>
<th>Population</th>
<th>Intervention</th>
<th>Follow-up (months)</th>
<th>Quality (SIGN- 50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arthur 2002</td>
<td>242</td>
<td>CABG patients</td>
<td>In addition to exercise, patients were telephoned every 2 weeks by the exercise specialist</td>
<td>6</td>
<td>High quality</td>
</tr>
<tr>
<td>Bambauer 2005</td>
<td>100</td>
<td>ACS patients</td>
<td>Six 30 minute telephone counseling sessions</td>
<td>6</td>
<td>Acceptable</td>
</tr>
<tr>
<td>Bazargani 2011</td>
<td>300</td>
<td>CABG patients</td>
<td>6 sessions (150 min/week) of psycho-education</td>
<td>3</td>
<td>Unacceptable</td>
</tr>
<tr>
<td>Beckie 1989</td>
<td>74</td>
<td>CABG patients</td>
<td>4 to 6 supportive-educative telephone calls with a cardiac rehabilitation nurse specialist</td>
<td>1.5</td>
<td>Acceptable</td>
</tr>
<tr>
<td>Gallagher 2003</td>
<td>196</td>
<td>Women with CAD</td>
<td>4 telephone calls to assist coping with recovery</td>
<td>3</td>
<td>Acceptable</td>
</tr>
<tr>
<td>Hanssen 2007</td>
<td>288</td>
<td>AMI patients</td>
<td>Nurse-initiated telephone calls after discharge</td>
<td>6</td>
<td>Acceptable</td>
</tr>
<tr>
<td>Hanssen 2009</td>
<td>288</td>
<td>AMI patients</td>
<td>Nurse-initiated telephone calls after discharge</td>
<td>18</td>
<td>Acceptable</td>
</tr>
<tr>
<td>Hartford 2002</td>
<td>166</td>
<td>CABG patients who have a caregiver</td>
<td>6 telephone calls to patients and partners</td>
<td>2</td>
<td>High quality</td>
</tr>
<tr>
<td>Holmes-Rovner 2008</td>
<td>525</td>
<td>ACS patients</td>
<td>Six-session telephone counseling calls by a health educator</td>
<td>8 months</td>
<td>Acceptable</td>
</tr>
<tr>
<td>Ma 2010</td>
<td>689</td>
<td>CAD patients</td>
<td>Pharmacist-delivered telephone counseling calls</td>
<td>12</td>
<td>Acceptable</td>
</tr>
<tr>
<td>Mclaughlin 2005</td>
<td>100</td>
<td>ACS patients with symptoms of depressive illness or anxiety</td>
<td>3-6 telephone counseling sessions of 30 minutes by clinicians</td>
<td>6</td>
<td>Acceptable</td>
</tr>
<tr>
<td>Mittag 2006</td>
<td>343</td>
<td>CAD patients</td>
<td>Monthly nurse-initiated telephone contacts</td>
<td>12</td>
<td>Acceptable</td>
</tr>
<tr>
<td>Neubeck 2009</td>
<td>208</td>
<td>ACS patients</td>
<td>A clinic visit plus 3 months of phone support</td>
<td>48</td>
<td>Acceptable</td>
</tr>
<tr>
<td>Neubeck 2011</td>
<td>208</td>
<td>ACS patients</td>
<td>1-hour consultation and telephone calls over 3 months</td>
<td>48</td>
<td>High quality</td>
</tr>
<tr>
<td>Redfern 2008</td>
<td>208</td>
<td>ACS patients</td>
<td>1-hour consultation and approximately four 10-minute follow-up calls</td>
<td>3</td>
<td>High quality</td>
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<tr>
<td>Redfern 2009</td>
<td>208</td>
<td>ACS patients</td>
<td>Clinic visit plus telephone support and tailored preferential risk modification</td>
<td>12</td>
<td>High quality</td>
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<td>Redfern 2010</td>
<td>208</td>
<td>ACS patients</td>
<td>One-hour initial consultation</td>
<td>12</td>
<td>High quality</td>
</tr>
<tr>
<td>Study</td>
<td>N</td>
<td>Patient group</td>
<td>Intervention</td>
<td>Duration</td>
<td>Quality</td>
</tr>
<tr>
<td>------------------</td>
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<td>--------------------------------</td>
<td>-----------------------------------------------------------------------------</td>
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</tr>
<tr>
<td>Reid 2007</td>
<td>100</td>
<td>CAD patients who were also current smokers</td>
<td>Automatic telephone contact plus counseling by up to three 20-min telephone sessions</td>
<td>12</td>
<td>High quality</td>
</tr>
<tr>
<td>Smith 2004</td>
<td>222</td>
<td>CABG patients</td>
<td>Exercise program and telephone follow-up every 2 weeks by an exercise specialist</td>
<td>12</td>
<td>High quality</td>
</tr>
<tr>
<td>Smith 2007</td>
<td>196</td>
<td>CABG patients</td>
<td>Exercise program and telephone follow-up every 2 weeks by an exercise specialist</td>
<td>72</td>
<td>High quality</td>
</tr>
<tr>
<td>Smith 2011</td>
<td>196</td>
<td>CABG patients</td>
<td>Exercise program and telephone follow-up every 2 weeks by an exercise specialist</td>
<td>72</td>
<td>High quality</td>
</tr>
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<td>Stevens 1985</td>
<td>59</td>
<td>MI patients</td>
<td>Received telephone calls by 2 nurses and the investigator</td>
<td>1.5-2</td>
<td>High quality</td>
</tr>
<tr>
<td>Tranmer 2004</td>
<td>200</td>
<td>CAD patients</td>
<td>Follow-up via nurse-initiated telephone calls</td>
<td>1.25</td>
<td>High quality</td>
</tr>
<tr>
<td>Vale 2002</td>
<td>245</td>
<td>CABG or PCI patients</td>
<td>Dietitian contacted patients 5 times by telephone regarding lipid levels</td>
<td>6</td>
<td>High quality</td>
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<tr>
<td>Vale 2003</td>
<td>792</td>
<td>CAD patients</td>
<td>Patients received coaching sessions by telephone</td>
<td>6</td>
<td>High quality</td>
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<tr>
<td>Van Elderen 1994</td>
<td>60</td>
<td>AMI patients</td>
<td>Nurse contacted the patient by telephone.</td>
<td>12</td>
<td>Acceptable</td>
</tr>
</tbody>
</table>

Note: CABG=Coronary artery bypass graft. ACS=Acute coronary syndrome. AMI=Acute myocardial infarction. CAD=Coronary artery disease. PCI=Percutaneous coronary intervention.
Figure 2. Risk of bias graph. Judgments made about each risk of bias item are presented as percentages across all included studies.
Clinical events

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Studies</th>
<th>$I^2$ (%)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>11</td>
<td>0</td>
<td>1.12 (0.71, 1.77)</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>4</td>
<td>15</td>
<td>0.62 (0.40, 0.97)</td>
</tr>
</tbody>
</table>

Risk factors (dichotomous outcomes)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Studies</th>
<th>$I^2$ (%)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medication adherence</td>
<td>2</td>
<td>61</td>
<td>0.93 (0.73, 1.20)</td>
</tr>
<tr>
<td>Smoking cessation</td>
<td>7</td>
<td>0</td>
<td>1.32 (1.07, 1.62)</td>
</tr>
</tbody>
</table>

Risk factors (continuous outcomes)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Studies</th>
<th>$I^2$ (%)</th>
<th>SMD (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL</td>
<td>4</td>
<td>58</td>
<td>-0.19 (-0.39, 0.00)</td>
</tr>
<tr>
<td>SBP</td>
<td>2</td>
<td>0</td>
<td>-0.22 (-0.40, -0.04)</td>
</tr>
</tbody>
</table>

Patient reported outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Studies</th>
<th>$I^2$ (%)</th>
<th>SMD (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety</td>
<td>5</td>
<td>29</td>
<td>-0.14 (-0.24, -0.04)</td>
</tr>
<tr>
<td>Depression</td>
<td>5</td>
<td>0</td>
<td>-0.10 (-0.21, -0.00)</td>
</tr>
<tr>
<td>QOL-MCS</td>
<td>3</td>
<td>57</td>
<td>0.01 (-0.23, 0.26)</td>
</tr>
<tr>
<td>QOL-PCS</td>
<td>3</td>
<td>0</td>
<td>0.12 (-0.03, 0.28)</td>
</tr>
</tbody>
</table>

Figure 3: Comparison of structured telephone support and usual care in terms of clinical events, risk factor modification and patient reported outcomes. LDL=Low-density lipoprotein. SBP=Systolic blood pressure. QOL-MCS=Quality of life (Mental Composite Score). QOL-PCS=Quality of life (Physical Composite Score).
Appendices

Appendix 1: Search strategies

**Medline**
1. exp telemedicine/
2. Speech Recognition Software/
3. Reminder Systems/
4. telemedicine.ab,ti.
5. "telemonitor*".ab,ti.
6. "home monitor*".ab,ti.
7. telecardiology.ab,ti.
8. telehealth.ab,ti.
9. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10. exp acute coronary syndrome/
11. exp coronary disease/
12. exp myocardial infarction/
13. exp angina pectoris/
15. "myocardial infarction".ab,ti.
16. acs.ab,ti.
17. "acute coronary syndrome".ab,ti.
18. "cardiac arrest".ab,ti.
19. "heart attack".ab,ti.
20. "heart infarction".ab,ti.
21. 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20
22. 9 and 21
23. randomized controlled trial.pt.
24. controlled clinical trial.pt.
25. randomized.ab.
26. placebo.ab.
27. clinical trials as topic.sh.
28. randomly.ab.
29. trial.ti.
30. 23 or 24 or 25 or 26 or 27 or 28 or 29
31. exp animals/ not humans.sh.
32. 30 not 31
33. 22 and 32

**EMBASE**
1. telemedicine/
2. telemedicine.ab,ti.
3. automatic speech recognition/
4. automatic speech recognition.ab,ti.
5. telecardiology/  
6. telecardiology.ab,ti.  
7. home monitoring/  
8. remot* monitor*.mp.  
9. telephone support.mp.  
10. reminder system/  
11. "telemonitor*".ab,ti.  
12. "home monitor*".ab,ti.  
13. telehealth/  
14. telehealth.ab,ti.  
15. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14  
16. ACS.mp.  
17. exp heart infarction/  
18. cardiac arrest.mp.  
19. exp angina pectoris/  
20. ischemic heart disease/ or acute coronary syndrome/ or angina pectoris/ or heart infarction/  
21. exp acute coronary syndrome/  
22. exp coronary disease/  
23. exp myocardial infarction/  
25. "myocardial infarction".ab,ti.  
26. acs.ab,ti.  
27. "acute coronary syndrome".ab,ti.  
28. "heart attack".ab,ti.  
29. "heart infarction".ab,ti.  
30. "cardiac arrest".ab,ti.  
31. 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30  
32. interactive voice response system/ or interactive voice response.mp.  
33. 15 or 32  
34. 31 and 33  
35. Clinical trial/  
36. Randomized controlled trial/  
37. Randomization/  
38. Single blind procedure/  
39. Double blind procedure/  
40. Crossover procedure/  
41. Placebo/  
42. Randomi?ed controlled trial$.tw.  
43. Rct.tw.  
44. Random allocation.tw.  
45. Randomly allocated.tw.  
46. Allocated randomly.tw.  
47. (allocated adj2 random).tw.  
49. Double blind$.tw.  
50. ((treble or triple) adj blind$).tw.
51. Placebo$.tw.
52. Prospective study/
53. or/35-52
54. Case study/
55. Case report.tw.
56. Abstract report/ or letter/
57. or/54-56
58. 53 not 57
59. 34 and 58

Cochrane

1. exp telemedicine/
2. Speech Recognition Software/
3. reminder Systems/
4. telemedicine.ab,ti.
5. "telemonitor*".ab,ti.
6. "home monitor*".ab,ti.
7. telecardiology.ab,ti.
8. telehealth.ab,ti.
9. telehealth/
10. telephone support.mp.
11. remot* monitor*.mp.
12. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11
13. exp acute coronary syndrome/
14. exp coronary disease/
15. exp myocardial infarction/
16. exp angina pectoris/
17. (coronary adj2 disease).ab,ti.
18. "myocardial infarction".ab,ti.
19. acs.ab,ti.
20. "acute coronary syndrome".ab,ti.
22. "heart attack".ab,ti.
23. "heart infarction".ab,ti.
24. cardiac arrest.mp.
25. ischemic heart disease/ or acute coronary syndrome/ or angina pectoris/ or heart infarction/
26. or/13-25
27. interactive voice response system/ or interactive voice response.mp.
28. 12 or 27
29. 26 and 28
AMED
1. exp telemedicine/
2. telemedicine.ab,ti.
3. "telemonitor".ab,ti.
4. "home monitor".ab,ti.
5. telehealth.ab,ti.
6. automatic speech recognition.ab,ti.
7. remot* monitor*.mp.
8. telephone support.mp.
9. interactive voice response system/ or interactive voice response.mp.
10. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
11. exp coronary disease/
12. exp myocardial infarction/
13. exp angina pectoris/
15. "myocardial infarction".ab,ti.
16. acs.ab,ti.
17. "acute coronary syndrome".ab,ti.
18. "cardiac arrest".ab,ti.
19. "heart attack".ab,ti.
20. ischemic heart disease/ or acute coronary syndrome/ or angina pectoris/ or heart infarction/
22. or/11-21
23. 10 and 22

PsychINFO
1. exp telemedicine/
2. telemedicine.ab,ti.
3. "telemonitor".ab,ti.
4. "home monitor".ab,ti.
5. telecardiology.ab,ti.
6. telehealth.ab,ti.
7. automatic speech recognition.ab,ti.
8. remot* monitor*.mp.
9. telephone support.mp.
10. telehealth/
11. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10
12. exp myocardial infarction/
13. exp angina pectoris/
15. "myocardial infarction".ab,ti.
16. acs.ab,ti.
17. "acute coronary syndrome".ab,ti.
18. "cardiac arrest".ab,ti.
19. "heart attack".ab,ti.
20. "heart infarction".ab,ti.
21. ischemic heart disease/ or acute coronary syndrome/ or angina pectoris/ or heart infarction/
22. 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21
23. 11 and 22

HealthStar
1. exp telemedicine/
2. Reminder Systems/
3. telemedicine.ab,ti.
4. "telemonitor*".ab,ti.
5. "home monitor*".ab,ti.
6. telecardiology.ab,ti.
7. telehealth.ab,ti.
8. automatic speech recognition.ab,ti.
9. remo*t monitor*.mp.
10. telephone support.mp.
11. interactive voice response system/ or interactive voice response.mp.
12. or/1-11
13. exp coronary disease/
14. exp myocardial infarction/
15. exp angina pectoris/
17. "myocardial infarction".ab,ti.
18. acs.ab,ti.
20. "cardiac arrest".ab,ti.
22. "heart infarction".ab,ti.
23. ACS.mp.
24. cardiac arrest.mp.
25. ischemic heart disease/ or acute coronary syndrome/ or angina pectoris/ or heart infarction/
26. or/13-25
27. 12 and 26
Table 2: Detailed description of included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Study population</th>
<th>Intervention/Comparison</th>
<th>Outcomes</th>
<th>Quality (Sign 50)</th>
</tr>
</thead>
</table>
| Arthur 2002    | This was a two-group randomized controlled Trial (N=242). | CABG patients                          | I: In addition to exercise, patients were telephoned every 2 weeks by the exercise specialist to monitor progress, assess and document adherence, revise the exercise prescription if necessary, and provide support and education.  
C: Hospital based exercise training | Patients were followed for 6 months. Primary outcome was peak exercise capacity. Secondary outcomes were health-related quality of life and social support. In addition, weight, waist to hip and consultations were recorded | ++    |
| Bambauer 2005  | This was a two-group randomized controlled Trial (N=100). | Patients aged 35 years or older who had a primary diagnosis of ACS defined as unstable angina pectoris or acute myocardial infarction met the inclusion criteria for the study. | I: six 30 minute telephone counseling sessions to identify cardiac-related fears  
C: Control patients received a short booklet on coping with chronic illness and were instructed to contact their primary care physician if they experienced any warning signs of more significant depression. | Patients were followed for 6 months. Global improvement scale (CGI-I scores) changes | +     |
| Bazargani 2011 | This was a two-group randomized controlled Trial (N=300). | Patients who attended 8 weeks rehabilitation program a month after CABG. | I: 6 sessions 150 min/week of psycho education  
C: no intervention detailed | Patients were followed for 3 months. General Adherence Scale and Special Adherence Scale (GAS-SAS) Cardiac Self-Efficacy Questionnaire (CSEQ) | -     |
| Beckie 1989    | This was a two-group randomized controlled Trial (N=74). | Patients scheduled for first-time nonemergency CABG surgery without additional cardiac surgical procedures and no major cardiac complications | I: support-educative telephone program between the participant and the cardiac rehabilitation nurse specialist through a series of 4 to 6 telephone calls  
C: Received routine in-hospital teaching available to all patients undergoing cardiac surgery. | Patients were followed for 1.5 months. Hospitalizations State anxiety scores | +     |
| Gallagher 2003 | This was a two-group randomized controlled Trial (N=196). | Eligible women diagnosed with myocardial infarction, coronary artery bypass grafts, coronary angioplasty, or stable angina (confirmed by angiography); without cardiac failure or unstable angina | I: The intervention began with an introductory session 1 to 2 days before hospital discharge and was followed by 4 telephone calls at 2 to 3 days, 1, 3, and 6 weeks postdischarge. Follow-up telephone calls were scheduled to assist women coping with various stages of adjustment during recovery.  
C: All inpatients received a Phase I education program, and all women were referred to local cardiac rehabilitation programs. | Patients were followed for 3 months. Psychosocial adjustment Anxiety Depression | +     |
| Hanssen 2007   | This was a two-group randomized controlled Trial (N=288). | Patients diagnosed with acute myocardial infarction (AMI) | I: Weekly nurse-initiated telephone calls were arranged for the first four weeks; subsequently calls were arranged six, eight, 12 and 24 weeks after discharge.  
C: All patients in the control group were managed in accordance with the current clinical practice, which encompassed one visit to a | Patients were followed for 6 months. health-related quality of life  
Secondary endpoints included | +     |
<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Participants</th>
<th>Intervention</th>
<th>Primary Endpoint</th>
<th>Secondary Endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hanssen 2009</td>
<td>This was a two-group randomized controlled Trial (N=288).</td>
<td>All patients admitted to the hospital with a diagnosis of AMI confirmed through medical records</td>
<td>I: Weekly nurse-initiated telephone calls were arranged for the first four weeks; subsequently calls were arranged six, eight, 12 and 24 weeks after discharge. C: All patients in the control group were managed in accordance with the current clinical practice, which encompassed one visit to a physician at the outpatient clinic 6–8 weeks after discharge, and subsequent visits to the patient’s general practitioner.</td>
<td>Patients were followed for 18 months. Primary endpoint was health-related quality of life. Secondary endpoints included smoking and exercise habits, return to work and rehospitalisation.</td>
<td></td>
</tr>
<tr>
<td>Hartford 2002</td>
<td>This was a two-group randomized controlled Trial (N=166).</td>
<td>Inclusion criteria for patients were as follows: (1) having a first elective CABG without valve replacement and (2) had a partner or family member at home involved in their care after discharge.</td>
<td>I: The intervention began on the day of discharge when patient and partner together were provided with information. This was followed by 6 telephone calls to patients and partners on days 1, 2, and 4, and weeks 1, 2, and 7 after discharge. C: The control group received usual care, which did not include systematic follow-up.</td>
<td>Patients were followed for 2 months. Anxiety.</td>
<td></td>
</tr>
<tr>
<td>Holmes-Rovner 2008</td>
<td>This was a two-group randomized controlled Trial (N=525).</td>
<td>Patient inclusion criteria were a working diagnosis of ACS in the medical record, a documented serum troponin I level greater than the upper limits of normal.</td>
<td>I: Patients received a six-session health behavior change telephone counseling program delivered by a trained health educator during the first three months after discharge. C: Patients received a written discharge contract listing recommended outpatient medications, cardiac rehabilitation recommendations, and health behavior changes (smoking cessation, diet modification, and exercise), as well as numerical values for ejection fraction and cholesterol.</td>
<td>Patients were followed for 8 months. All-cause mortality. Attempt of weight loss. Attempt of smoking cessation. Physical activity (150 min/week).</td>
<td></td>
</tr>
<tr>
<td>Ma 2010</td>
<td>This was a two-group randomized controlled Trial (N=689).</td>
<td>A patient was eligible for the study if he/she was between the ages of 30 and 85 years and had CHD defined as the presence of at least one coronary lesion ≥50% at the time of coronary angiography. Patients could have a history of prior CHD, or this could have been their first such diagnosis.</td>
<td>I: The pharmacist-delivered telephone counseling calls took place at two weeks, and at 1, 3, 6, and 9 months following discharge. C: consisted of normal clinical care as determined by the patient's provider.</td>
<td>Patients were followed for 12 months. Proportion achieving LDL-C &lt;100 mg/dl. Adherence to statin use (CMA). Total cholesterol LDL HDL TG.</td>
<td></td>
</tr>
<tr>
<td>McLaughlin 2005</td>
<td>This was a two-group randomized controlled Trial (N=100).</td>
<td>Acute coronary syndrome (ACS) patients aged 35 or older, who are able to speak English, and have access to a touch-tone phone, and have symptoms of depressive illness or anxiety.</td>
<td>I: Sessions were 30 minutes and conducted by doctoral-level clinicians (a psychiatrist, clinical psychologist, and internist). Patients were expected to complete 6 sessions but allowed to participate in as few as 3 if the therapist and patient agreed that all issues set forth during treatment were reviewed, and that treatment goals were reached. C: Patients received a booklet on coping with cardiac illness typical of those given at hospital discharge and were instructed to contact their primary care physician if they experienced any warning signs of depression.</td>
<td>Patients were followed for 6 months. Death. Depression &amp; Anxiety (HADS).</td>
<td></td>
</tr>
<tr>
<td>Mittag 2006</td>
<td>This was a two-group randomized controlled Trial (N=343).</td>
<td>Patients who previously had suffered from a cardiac event (myocardial infarction, coronary artery bypass grafting, percutaneous coronary intervention)</td>
<td>I: The intervention consisted of monthly nurse-initiated telephone contacts. It was manual-based, and included individually tailored counselling on sports and physical exercise, nutrition, non-smoking, and stress management and psychosocial issues; also medical (cardiac) problems</td>
<td>Patients were followed for 12 months. All-cause mortality. Total cholesterol. HDL Blood pressure.</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Study Design</td>
<td>Population</td>
<td>Intervention</td>
<td>Follow-up</td>
<td>Outcome Measures</td>
</tr>
<tr>
<td>-------</td>
<td>--------------</td>
<td>------------</td>
<td>--------------</td>
<td>-----------</td>
<td>-----------------</td>
</tr>
<tr>
<td>Neubeck 2009</td>
<td>This was a two-group randomized controlled Trial (N=208).</td>
<td>ACS survivors</td>
<td>C: The control group received six flyers on general health topics (relaxation, sports and physical exercise, sleep disorders, low back pain, nutrition) by mail every second month as an attention placebo. Patients in the intervention group were given the same written information</td>
<td>Patients were followed for 48 months. Total cholesterol Systolic blood pressure BMI Smoker (%) Inactive (%) Proportion of patients with ≥3 risk factors</td>
<td>Depression Anxiety Proportion of smokers</td>
</tr>
<tr>
<td>Neubeck 2011</td>
<td>This was a two-group randomized controlled Trial (N=208).</td>
<td>ACS survivors</td>
<td>I: non CR attending CHOICE intervention which comprises tailored risk factor reduction packaged as a clinic visit plus 3 months of phone support C: non CR attending UC group (usual followup) C2: not randomized CR attending group (exercise and education sessions)</td>
<td>Patients were followed for 48 months. All-cause mortality Total Cholesterol and proportion at &gt;4mmol/l target LDL and proportion at 2.5mmol/l target SBP and proportion at 140 mmHg target BMI and proportion at ≥30 kg/m2 Physical activity and proportion inactive Proportion of current smokers Proportion with ≥3 risk factors Proportion taking statins Cardiac depression score and proportion at score &gt;100</td>
<td>++</td>
</tr>
<tr>
<td>Redfern 2008</td>
<td>This was a two-group randomized controlled Trial (N=208).</td>
<td>Diagnosis of ACS in the 6 months before recruitment</td>
<td>I: The CHOICE patients participated in ongoing conventional health care and a 3-month modular patient-centered program. The CHOICE program includes a 1-h initial consultation and multiple telephone calls over 3 months. C: ongoing conventional health care. Managing cardiovascular health in consultation with their GP and cardiologist. C2: non-randomized group participated in traditional facility-based CR. The 6-week CR program included two group-based 60-min exercise sessions per week and a weekly 2-h education session.</td>
<td>Patients were followed for 3 months. All-cause mortality Proportion with no risk factors Proportion with ≥3 or more risk factors Continuous: QOL Physical activity Systolic BP TC TG LDL-C BMI</td>
<td>++</td>
</tr>
<tr>
<td>Redfern 2009</td>
<td>This was a two-group randomized controlled Trial (N=208).</td>
<td>ACS survivors</td>
<td>I: intervention included a 1-hour initial consultation and approximately four 10-minute follow-up phone calls over 3 months C: Participants continued to manage their cardiovascular health as directed by their family physician often in consultation with their cardiologist. C2: Nonrandomized reference group participating in CR - The rehabilitation group participated in standard phase 2 CR that included two 60-minute gymnasium sessions and a 2-hour education session each week for 6 weeks.</td>
<td>Patients were followed for 12 months. All-cause mortality Proportion Visiting a cardiologist number with 3 or more risk factors</td>
<td>++</td>
</tr>
<tr>
<td>Reference</td>
<td>Study Design</td>
<td>Participants</td>
<td>Intervention</td>
<td>Outcomes</td>
<td></td>
</tr>
<tr>
<td>-----------</td>
<td>--------------</td>
<td>--------------</td>
<td>--------------</td>
<td>----------</td>
<td></td>
</tr>
<tr>
<td>Redfern 2010</td>
<td>This was a two-group randomized controlled Trial (N=208).</td>
<td>ACS survivors</td>
<td>I: patients participated in a three-month, patient-centred modular secondary prevention program including a one-hour initial consultation and four × 10 minute (average) follow-up phone calls over three months. C: participated in ongoing conventional care, aimed at managing their cardiovascular health as directed by their General Practitioner, ideally in consultation with their Cardiologist.</td>
<td>Patients were followed for 12 months. Medical consultations</td>
<td></td>
</tr>
<tr>
<td>Reid 2007</td>
<td>This was a two-group randomized controlled Trial (N=100).</td>
<td>Participants were current smokers (5 cigarettes per day) over the age of 18 years, hospitalized at UOHI for acute coronary syndrome (ACS), elective PCI or diagnostic catheterization related to CHD.</td>
<td>I: Participants were automatically contacted via telephone on days 3, 14 and 30 post-hospital discharge to check the patient’s smoking status and assess the risk of relapse. In addition, telephone counseling consisted of up to three 20-min telephone counseling sessions over an 8-week period if patients were considered to need them. C: All participants received advice to quit smoking; access to Nicotine Replacement Therapy during hospitalization (if necessary); brief bedside counseling with a nurse-specialist; a self-help guide; and the provision of information about the hospital’s outpatient smoking cessation program and other community programs.</td>
<td>Patients were followed for 12 months. All-cause mortality Smoking abstinence</td>
<td></td>
</tr>
<tr>
<td>Smith 2004</td>
<td>This was a two-group randomized controlled Trial (N=222).</td>
<td>CABG</td>
<td>I: Patients received a home based exercise exercise program and patients were telephoned every 2 weeks by the exercise specialist to monitor progress, assess and document adherence, revise the exercise prescription if necessary, and provide support and education. C: Patients assigned to the Hospital based exercise group were expected to attend supervised exercise sessions 3 times per week for 6 months.</td>
<td>Patients were followed for 12 months. Physical capacity (VO2) Peak Mets Peak work rate BMI Waist to hip HRQOL Social support Habitual physical activity (using the Physical Activity Scale for the Elderly [PASE])</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>Intervention</td>
<td>Control</td>
<td>Outcomes</td>
<td></td>
</tr>
<tr>
<td>-------</td>
<td>--------</td>
<td>--------------</td>
<td>---------</td>
<td>----------</td>
<td></td>
</tr>
<tr>
<td>Smith 2007</td>
<td>This was a two-group randomized controlled Trial (N=196).</td>
<td>Patients received a home based exercise program and patients were telephoned every 2 weeks by the exercise specialist to monitor progress, assess and document adherence, revise the exercise prescription if necessary, and provide support and education.</td>
<td>Patients assigned to the Hospital based exercise group were expected to attend supervised exercise sessions 3 times per week for 6 months.</td>
<td>Patients were followed for 72 months. All-cause mortality Nonfatal clinical events Myocardial infarction Patients hospitalized Number of hospitalizations Smoking status Exercise capacity (peak VO2) Peak METs Peak work rate Exercise maintenance Total cholesterol LDL HDL TG BMI Waist to hip ratio Habitual physical activity ++</td>
<td></td>
</tr>
<tr>
<td>Smith 2011</td>
<td>This was a two-group randomized controlled Trial (N=196).</td>
<td>Patients received a home based exercise program and patients were telephoned every 2 weeks by the exercise specialist to monitor progress, assess and document adherence, revise the exercise prescription if necessary, and provide support and education.</td>
<td>Patients assigned to the Hospital based exercise group were expected to attend supervised exercise sessions 3 times per week for 6 months.</td>
<td>Patients were followed for 72 months. All-cause mortality Nonfatal clinical events Myocardial infarction Patients reporting a hospitalization Total number of hospitalizations Exercise capacity (VO2) Exercise maintenance Habitual physical activity weight and waist to hip ratio ++</td>
<td></td>
</tr>
<tr>
<td>Stevens 1985</td>
<td>This was a two-group randomized controlled Trial (N=59).</td>
<td>Patients entering coronary care unit with a diagnosis of MI.</td>
<td>Nurses educated MI patients prior to discharge and all got a booklet to take home. Upon discharge patients were returned to the care of the GP and received usual followup.</td>
<td>Patients were followed for 1.5-2 months. Knowledge ++</td>
<td></td>
</tr>
<tr>
<td>Tranmer 2004</td>
<td>This was a two-group randomized controlled Trial (N=200).</td>
<td>Patients were approached for participation if they had undergone their first elective or emergent cardiac surgery. Had no unexpected cardiac complications that necessitated an unexpected stay in the Intensive Care Unit (ICU).</td>
<td>Patients were active and ongoing follow-up via nurse-initiated telephone calls at 3 and 5 days following hospital discharge, then weekly for 4 more weeks. Telephone sessions were individually tailored in response to patient’s symptoms, concerns, and recovery.</td>
<td>Patients were followed for 1.25 months. Unexpected hospital admissions HRQOL Distress Satisfaction with care Proportion with at ++</td>
<td></td>
</tr>
</tbody>
</table>
### Vale 2002

**This was a two-group randomized controlled Trial (N=245).**

Patients with CHD who had been hospitalized for revascularization procedures, either coronary artery bypass graft surgery (CABG) or percutaneous coronary intervention (PCI).

| I: Coaching was performed by a dietitian experienced in working with patients with cardiovascular disease. The coach initiated contact with the patient by telephone at 2 weeks postrandomization for the first coaching session. A further three phone coaching sessions followed at 6-week intervals. A fifth call at 24 weeks was made to patients in the coaching group advising them to obtain the 6-month blood sample for serum lipid analysis. |
| C: All patients in the study (including patients in the coaching intervention group) were offered information about a cardiac rehabilitation program and were encouraged to attend. Patients in the usual care group were contacted at 24 weeks postrandomization to obtain a fasting serum lipid profile within the next 2 weeks. |

**Patients were followed for 6 months. All-cause mortality Adherence at an outpatient CR program Total cholesterol (mean) LDL-C (mean)** ++

### Vale 2003

**This was a two-group randomized controlled Trial (N=792).**

Patients Included if they had been hospitalized for 1) CABG 2) PCI 3) AMI or unstable angina and then discharged on medical therapy or 4) Coronary angiography with planned (elective) revascularization

| I: A program package was mailed to patients. The package included information and a 1-page chart of risk factor targets for CHD secondary prevention. The chart was sent to the usual medical caregiver as well. They also received coaching sessions by telephone within 2 weeks after randomization, 3 further telephone coaching sessions at 6 week intervals and a 5th call at 24 weeks |
| C: Patients received a hospital discharge summary, a one page chart of risk factor for CHD secondary prevention to them and their medical caregivers as well as contacted once after discharge at 24 weeks for follow-up assessment |

**Patients were followed for 6 months. All-cause mortality Adherence (number taking lipid lowering drug therapy) Change in: Total Cholesterol LDL Systolic Depression (Cardiac depression scale) Anxiety (state trait anxiety inventory) weight WHR** ++

### Van Elderen 1994

**This was a two-group randomized controlled Trial (N=80).**

Patients admitted for acute myocardial infarction.

| I: After discharge: once a week and for 6 weeks after discharge from hospital until the first check up with cardiologist (typically 8 weeks after discharge) a nurse contacted the patient by telephone. |
| C: Patients received standard medical care only; consisting primarily of medical care. A standard physical rehabilitation program was implemented in the nursing ward. |

**Patients were followed for 12 months. All-cause mortality Smoking cessation Anxiety Vital exhaustion and depression** +

---

*Note: High quality (++); Acceptable (+); Unacceptable (-). CABG=Coronary artery bypass graft. ACS=Acute coronary syndrome. AMI=Acute myocardial infarction. CAD=Coronary artery disease. PCI=Percutaneous coronary intervention.*
Appendix 3: Risk of bias summary

Figure 4. Risk of bias summary: review authors’ judgments about each risk of bias item for each included study.
Appendix 4: Data and Analysis

Figure 5: Analysis 1.1. Comparison of structured telephone support and usual care in CAD on all-cause mortality.

Figure 6: Analysis 1.2. Sensitivity analysis by patient characteristics comparing structured telephone support and usual care in CAD on all-cause mortality.
Figure 7: Analysis 1.3. Comparison of structured telephone support and usual care in CAD on hospitalization.

Figure 8: Analysis 1.4. Comparison of structured telephone support and usual care in CAD on smoking cessation.

Figure 9: Analysis 1.5. Comparison of structured telephone support and usual care in CAD on medication adherence.
<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Telephone group Mean</th>
<th>SD</th>
<th>Total</th>
<th>Control group Mean</th>
<th>SD</th>
<th>Total</th>
<th>Std. Mean Difference IV, Random, 95% CI Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vale 2002</td>
<td>3.11</td>
<td>1</td>
<td>121</td>
<td>3.57</td>
<td>1</td>
<td>124</td>
<td>-0.46 [-0.71, -0.20] 2002</td>
</tr>
<tr>
<td>Smith 2007</td>
<td>3.21</td>
<td>0.3</td>
<td>70</td>
<td>2.3</td>
<td>0.9</td>
<td>74</td>
<td>-0.23 [-0.50, 0.04] 2007</td>
</tr>
<tr>
<td>Ng 2010</td>
<td>94.7</td>
<td>31.3</td>
<td>351</td>
<td>97.79</td>
<td>35.1</td>
<td>338</td>
<td>-9.92 [-11.72, -8.12] 2010</td>
</tr>
<tr>
<td>Neubeck 2011</td>
<td>2.2</td>
<td>0.0511</td>
<td>72</td>
<td>2.2</td>
<td>0.0511</td>
<td>72</td>
<td>0.00 [-0.43, 0.43] 2011</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>614</td>
<td>608</td>
<td>100.0%</td>
<td>-0.19 [-0.39, 0.00]</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.02, CHI² = 7.87, df = 3 (P = 0.07); I² = 50%
Test for overall effect Z = 1.96 (P = 0.05)

Figure 10: Analysis 1.6. Comparison of structured telephone support and usual care in CAD on low-density lipoprotein.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Telephone group Mean</th>
<th>SD</th>
<th>Total</th>
<th>Control group Mean</th>
<th>SD</th>
<th>Total</th>
<th>Std. Mean Difference IV, Random, 95% CI Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vale 2002</td>
<td>3.11</td>
<td>1</td>
<td>121</td>
<td>3.57</td>
<td>1</td>
<td>124</td>
<td>-0.46 [-0.71, -0.20] 2002</td>
</tr>
<tr>
<td>Smith 2007</td>
<td>3.21</td>
<td>0.3</td>
<td>70</td>
<td>2.3</td>
<td>0.9</td>
<td>74</td>
<td>-0.23 [-0.50, 0.04] 2007</td>
</tr>
<tr>
<td>Ng 2010</td>
<td>94.7</td>
<td>31.3</td>
<td>351</td>
<td>97.79</td>
<td>35.1</td>
<td>338</td>
<td>-9.92 [-11.72, -8.12] 2010</td>
</tr>
<tr>
<td>Neubeck 2011</td>
<td>2.2</td>
<td>0.0511</td>
<td>72</td>
<td>2.2</td>
<td>0.0511</td>
<td>72</td>
<td>0.00 [-0.43, 0.43] 2011</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>483</td>
<td>484</td>
<td>100.0%</td>
<td>-0.10 [-0.23, 0.03]</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.00, CHI² = 1.00, df = 2 (P = 0.61); I² = 0%
Test for overall effect Z = 1.56 (P = 0.12)

Figure 11: Analysis 1.7. Sensitivity analysis by duration of follow-up comparing structured telephone support and usual care in CAD on low-density lipoprotein.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Telephone group Mean</th>
<th>SD</th>
<th>Total</th>
<th>Control group Mean</th>
<th>SD</th>
<th>Total</th>
<th>Std. Mean Difference IV, Random, 95% CI Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Milbag 2008</td>
<td>132.0</td>
<td>17.1</td>
<td>171</td>
<td>138.1</td>
<td>20.6</td>
<td>172</td>
<td>-0.22 [-0.43, -0.00] 2008</td>
</tr>
<tr>
<td>Neubeck 2011</td>
<td>132.8</td>
<td>20</td>
<td>72</td>
<td>138.8</td>
<td>17.87</td>
<td>72</td>
<td>-0.24 [-0.56, 0.09] 2011</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>243</td>
<td>244</td>
<td>100.0%</td>
<td>-0.22 [-0.40, -0.04]</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.00; CHI² = 0.01, df = 1 (P = 0.92); I² = 0%
Test for overall effect Z = 2.44 (P = 0.01)

Figure 12: Analysis 1.8. Comparison of structured telephone support and usual care in CAD on systolic blood pressure.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Telephone group Mean</th>
<th>SD</th>
<th>Total</th>
<th>Control group Mean</th>
<th>SD</th>
<th>Total</th>
<th>Std. Mean Difference IV, Random, 95% CI Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trimmer 2004</td>
<td>36.3</td>
<td>6.4</td>
<td>102</td>
<td>36.2</td>
<td>7.5</td>
<td>98</td>
<td>0.01 [-0.26, 0.28] 2004</td>
</tr>
<tr>
<td>Smith 2007</td>
<td>44.8</td>
<td>10.3</td>
<td>70</td>
<td>42.5</td>
<td>10.5</td>
<td>74</td>
<td>0.22 [-0.11, 0.55] 2007</td>
</tr>
<tr>
<td>Hansen 2009</td>
<td>50.73</td>
<td>8.62</td>
<td>158</td>
<td>49.46</td>
<td>8.45</td>
<td>132</td>
<td>0.15 [-0.08, 0.38] 2009</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>328</td>
<td>304</td>
<td>100.0%</td>
<td>0.12 [-0.03, 0.28]</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.00; CHI² = 0.97, df = 2 (P = 0.62); I² = 0%
Test for overall effect Z = 1.53 (P = 0.13)

Figure 13: Analysis 1.9. Comparison of structured telephone support and usual care in CAD on quality of life physical composite score.
Figure 14: Analysis 2.0. Comparison of structured telephone support and usual care in CAD on quality of life mental composite score.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Telephone group Mean</th>
<th>Telephone group SD</th>
<th>Telephone group Total</th>
<th>Control group Mean</th>
<th>Control group SD</th>
<th>Control group Total</th>
<th>Weight</th>
<th>Std. Mean Difference IV, Random, 95% CI</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trummer 2004</td>
<td>50.4</td>
<td>11.5</td>
<td>102</td>
<td>51.7</td>
<td>11.9</td>
<td>98</td>
<td>33.3%</td>
<td>-0.11 [-0.39, 0.17]</td>
<td>2004</td>
</tr>
<tr>
<td>Smith 2007</td>
<td>54.5</td>
<td>7.6</td>
<td>70</td>
<td>51.7</td>
<td>10.3</td>
<td>74</td>
<td>28.3%</td>
<td>0.31 [0.02, 0.64]</td>
<td>2007</td>
</tr>
<tr>
<td>Hjortland 2008</td>
<td>50.1</td>
<td>13.5</td>
<td>158</td>
<td>50.97</td>
<td>9.56</td>
<td>132</td>
<td>38.4%</td>
<td>-0.10 [-0.33, 0.14]</td>
<td>2008</td>
</tr>
<tr>
<td>Total (5%)</td>
<td>328</td>
<td></td>
<td></td>
<td>304</td>
<td></td>
<td></td>
<td></td>
<td>0.01 [-0.23, 0.26]</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.03; Chi² = 4.60, df = 2 (P = 0.10), I² = 57%
Test for overall effect: Z = 0.10 (P = 0.92)

Figure 15: Analysis 2.1. Comparison of structured telephone support and usual care in CAD on depression.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Telephone group Mean</th>
<th>Telephone group SD</th>
<th>Telephone group Total</th>
<th>Control group Mean</th>
<th>Control group SD</th>
<th>Control group Total</th>
<th>Weight</th>
<th>Std. Mean Difference IV, Random, 95% CI</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Van Elderen 1994</td>
<td>23.23</td>
<td>6.18</td>
<td>30</td>
<td>25.15</td>
<td>7.58</td>
<td>36</td>
<td>4.0%</td>
<td>-0.27 [-0.78, 0.23]</td>
<td>1994</td>
</tr>
<tr>
<td>Gallagher 2003</td>
<td>4.0</td>
<td>4.6</td>
<td>103</td>
<td>4.2</td>
<td>103</td>
<td>13.3%</td>
<td>0.05 [0.24, 0.33]</td>
<td>2003</td>
<td></td>
</tr>
<tr>
<td>Vale 2003</td>
<td>-4.8</td>
<td>27.31</td>
<td>398</td>
<td>-2.8</td>
<td>19.18</td>
<td>394</td>
<td>53.2%</td>
<td>-0.10 [-0.24, 0.04]</td>
<td>2003</td>
</tr>
<tr>
<td>McLaughlin 2005</td>
<td>5.7</td>
<td>3.6</td>
<td>33</td>
<td>8.6</td>
<td>3.9</td>
<td>67</td>
<td>6.7%</td>
<td>-0.24 [-0.63, 0.16]</td>
<td>2005</td>
</tr>
<tr>
<td>Kibler 2006</td>
<td>11.5</td>
<td>8.8</td>
<td>171</td>
<td>12.1</td>
<td>8.9</td>
<td>172</td>
<td>23.0%</td>
<td>-0.13 [-0.34, 0.09]</td>
<td>2006</td>
</tr>
<tr>
<td>Total (5%)</td>
<td>745</td>
<td></td>
<td></td>
<td>746</td>
<td></td>
<td></td>
<td></td>
<td>0.10 [0.21, 0.00]</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.00; Chi² = 2.00, df = 4 (P = 0.73); I² = 0%
Test for overall effect: Z = 2.02 (P = 0.04)

Figure 16: Analysis 2.2. Comparison of structured telephone support and usual care in CAD on anxiety.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Telephone group Mean</th>
<th>Telephone group SD</th>
<th>Telephone group Total</th>
<th>Control group Mean</th>
<th>Control group SD</th>
<th>Control group Total</th>
<th>Weight</th>
<th>Std. Mean Difference IV, Random, 95% CI</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enelow 1989</td>
<td>29.78</td>
<td>7.72</td>
<td>37</td>
<td>43.22</td>
<td>11.52</td>
<td>37</td>
<td>12.8%</td>
<td>-1.38 [-1.86, -0.90]</td>
<td>1989</td>
</tr>
<tr>
<td>Van Elderen 1994</td>
<td>37.00</td>
<td>12.12</td>
<td>30</td>
<td>39.00</td>
<td>14.44</td>
<td>34</td>
<td>12.8%</td>
<td>-0.10 [-0.70, 0.51]</td>
<td>1994</td>
</tr>
<tr>
<td>Vale 2003</td>
<td>-2.2</td>
<td>8.113</td>
<td>396</td>
<td>-1.1</td>
<td>7.0674</td>
<td>394</td>
<td>21.3%</td>
<td>-0.14 [-0.29, -0.00]</td>
<td>2003</td>
</tr>
<tr>
<td>Gallagher 2003</td>
<td>5.7</td>
<td>5.2</td>
<td>103</td>
<td>5.6</td>
<td>93</td>
<td>16.2%</td>
<td>0.14 [0.04, 0.42]</td>
<td>2003</td>
<td></td>
</tr>
<tr>
<td>McLaughlin 2005</td>
<td>6.3</td>
<td>3.5</td>
<td>53</td>
<td>7.3</td>
<td>47</td>
<td>15.4%</td>
<td>-0.13 [-0.598, 0.20]</td>
<td>2005</td>
<td></td>
</tr>
<tr>
<td>Milag 2006</td>
<td>50.3</td>
<td>11.3</td>
<td>154</td>
<td>10.8</td>
<td>143</td>
<td>19.5%</td>
<td>-0.24 [-0.52, -0.00]</td>
<td>2006</td>
<td></td>
</tr>
<tr>
<td>Total (5%)</td>
<td>775</td>
<td></td>
<td></td>
<td>744</td>
<td></td>
<td></td>
<td></td>
<td>0.29 [0.56, -0.01]</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.00; Chi² = 28.81, df = 5 (P < 0.0001); I² = 81%
Test for overall effect: Z = 2.04 (P = 0.04)
Figure 17: Analysis 2.3. Sensitivity analysis by patient characteristics comparing structured telephone support and usual care in CAD on anxiety.

Figure 18: Analysis 2.4. Fixed effects model comparison of structured telephone support and usual care in CAD on anxiety.

Figure 19: Analysis 2.5. Sensitivity analysis by greater than 6 months of follow-up comparing structured telephone support and usual care in CAD on anxiety.
CHAPTER FOUR: A NETWORK META-ANALYSIS

The following is a manuscript prepared for publication, based on a network meta-analysis that compared the impact of various telemedicine interventions on clinical events in individuals with heart failure. While the previous manuscript determined that a basic form of telemedicine was effective compared to usual care in individuals with coronary artery diseases that did not advance to heart failure, the objective of this manuscript was to compare interventions that have never been compared in the literature to determine if the more complex forms of telemedicine could effectively reduce clinical events in patients with heart failure and how these interventions could rank in effectiveness against one another.

A copy of The SIGN-50 Checklist used to assess the methodological quality of the included studies and a copy of The AMSTAR Checklist used to assess the methodological quality of the included reviews are provided in Appendix B and C of the thesis, respectively.

This manuscript was co-authored by the student (AK), his supervisor, Dr. George A. Wells, Chris Cameron and Dr. Shu-Ching Hsieh. The student is first author of this paper, having been primarily responsible for the conception of the study, data collection, analysis and the writing of the manuscript. Dr. Wells provided guidance throughout the process. Chris Cameron provided valuable feedback during the analysis of the data. Dr. Hsieh was integral for the stages of study selection and data extraction.
Health outcomes associated with various telemedicine Interventions in patients with Heart Failure (HF): A network meta-analysis.

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Keywords: heart failure, telemedicine, cardiac rehabilitation.

Total word count: 3,461 words (text only)

This manuscript includes one (1) table, five (5) figures, and thirteen (13) appendices.
Abstract

Background: Most of the evidence available on the effectiveness of telemedicine interventions for patients with heart failure has come from studies that compared one form of telemedicine with standard care. As such, there is a lack of evidence with regards to how effective these active interventions are compared to one another. To combine direct within-trial comparisons with indirect evidence from other trials, a network meta-analysis is needed. Using this method, indirect comparisons preserve the within-trial randomized results and are constructed from trials that have at least one treatment in common. In using all the available evidence, conducting a network meta-analysis can provide greater precision for the aforementioned direct comparisons. It also provides estimates for head-to-head comparisons that have not yet been made provided that there is a common comparator.

Methods: Systematic reviews that examined the impact of telemedicine interventions on heart failure patients were identified using the following databases: The Cochrane Library, MEDLINE, EMBASE and CINAHL. Randomized controlled trials (RCTs), from identified reviews, were included into the network meta-analysis if they examined the outcomes mortality, hospitalization and heart failure related hospitalization for five main forms of telemedicine interventions in heart failure patients. For direct comparisons, pairwise meta-analyses were conducted. Mixed treatment comparisons using Bayesian methods were carried out to incorporate data from indirect evidence.

Results: Eight systematic reviews were identified and 30 RCTs (N=10,193 patients) were included in the network meta-analysis. Compared to usual care, the only interventions that reduced deaths were structured telephone support [Odds Ratio (OR) 0.7972 and 95% Credible
Intervals (CI) (0.6589, 0.9603) and telemonitoring [OR 0.5312 (0.3634, 0.7969)]. No interventions were found to be effective in reducing all-cause hospitalizations. However, structured telephone support [OR 0.6911 (0.5621, 0.8462)], telemonitoring [OR 0.6374 (0.3932, 0.9479)] and telemedicine that included the transmission of electrocardiographic data [OR 0.7083 (0.5161, 0.9805)] all reduced hospitalizations due to heart failure compared to usual care. Across the aforementioned outcomes, no other comparisons were found to favor one form of telemedicine over the other.

**Conclusion:** This study demonstrates that both structured telephone support and telemonitoring interventions may help reduce the outcomes of death and heart failure related hospitalizations. For this particular population however, telemonitoring is the best intervention.
Introduction

Several studies and reviews have examined the impact of using telemedicine interventions to deliver remote specialized cardiovascular care to a large number of patients with heart failure. Compared to usual care, current research has shown that the use of telemedicine had no significant effect on all-cause hospital admissions but did significantly reduce all-cause mortality and hospital admissions related to heart failure.\(^1\)\(^-\)\(^4\) Although such interventions will require an initial financial investment, they will likely lead to substantially reduced costs in the long term particularly by reducing readmissions and travel costs.\(^5\)

These findings have been recently challenged when data from a large multicenter randomized controlled trial found no reduction associated with telemonitoring when compared to usual care in the risk of heart failure readmission, readmission from any cause or death.\(^6\) The inconclusiveness of the evidence may be attributed to a number of reasons. Generally, the criteria used by reviewers to define telemedicine have led to the inclusion of a wide range of interventions that vary in their intensity, invasiveness and complexity. The interventions considered included: Structured telephone support (STS) which involves regular follow-up calls between the health professional and the patient; Telemonitoring systems which involve the transmission of information on symptoms and signs (TM); Telemonitoring systems and regular telephone follow-up combined (RPM); Telemedicine systems involving video monitoring (VIDEO); and Telemedicine systems involving electrocardiographic transmissions (ECG).

In most cases, the comparator considered was “standard” or “usual” care. This definition also varied significantly across studies and reviews. These clinical differences could lead to difficulties in combining and comparing results and as a consequence, it has been difficult to
identify the potential benefits of each unique telemedicine intervention. The lack of direct head-to-head comparison across these different interventions also makes it difficult for physicians to determine which form of telemedicine is considered to be most effective.

Network meta-analysis, also known as mixed-treatment comparisons meta-analysis or multiple-treatments meta-analysis would allow the integration of data from direct (when treatments are compared within a randomized trial) and indirect comparisons (when treatments are compared between trials by combining results on how effective they are compared with a common comparator treatment). Simultaneously integrating data using this method allows for greater precision when calculating effect estimates. A network meta-analysis will be conducted to examine the impact of the various strategies of telemedicine interventions on the outcomes of death, all-cause hospitalization and heart failure hospitalization in heart failure patients.

**Methods**

**Search strategy and selection criteria:** Relevant systematic reviews of randomized controlled trials listed before December 2012 were identified by searching the following databases: The Cochrane Library, MEDLINE, EMBASE and CINAHL. The search strategies are described in Appendix 1. Reviews were included if they examined the impact of telemedicine interventions in adult heart failure patients. Randomized controlled trials from identified reviews were included in the network meta-analysis if they provided patient data on all-cause mortality, all-cause hospitalization or heart failure hospitalization in heart failure patients who received either usual care or any of the aforementioned five forms of telemedicine interventions. Study selection was conducted by two independent reviewers.
**Quality assessment:** The AMSTAR tool\(^{10}\) was used to assess the quality of included systematic reviews. The quality of included randomized controlled trials was assessed using the SIGN-50 checklist\(^{11}\) which examines the internal validity of randomized trials by evaluating randomization, concealment of allocation, and inclusion of all patients randomly assigned to treatment groups in the analysis according to the intention-to-treat principle.

**Statistical analyses:** Both Bayesian network meta-analyses and traditional frequentist pairwise meta-analyses were conducted. Individual trial data were used, which were extracted from the identified systematic reviews. Pair-wise meta-analyses were conducted by analyzing studies that compared the same interventions with a random-effects model. Heterogeneity was investigated by examining both forest plots and the inconsistency index \(I^2\). \(^{13}\) \(I^2\) values of less than 25% represented mild heterogeneity, between 25% and 50% represented moderate heterogeneity, and greater than 50% represented considerable heterogeneity. Results having a \(p\)-value of less than 0.05 and 95% confidence intervals (CIs) that excluded 1 were considered to be statistically significant. These analyses were carried out using Comprehensive Meta-Analysis and Review Manager of the Cochrane Collaboration.

For the primary analysis, the frequency data from each trial were used in the network meta-analysis.\(^{12}\) WinBUGS software (MRC Biostatistics Unit, Cambridge, UK) was used to conduct Bayesian network meta-analysis (NMA) using a binomial likelihood model, which allows for the use of multi-arm trials. Vague priors were assigned for basic parameters throughout the NMA. Three chains were fit in WinBUGS for each analysis, with 40,000 iterations, and a burn-in of 40,000 iterations.
Assessment of model fit for NMA comprised of assessment of the deviance information criterion (DIC) and the residual deviance. Models with smaller DIC were preferred to models with larger DIC. Similarly, the total value for the residual deviance should be lower than the number of unconstrained data points. To ensure convergence was reached, Brooks-Gelman-Rubin plots were assessed. Model convergence is evident when the Gelman-Rubin statistic approaches 1. To examine inconsistency, the deviances were plotted and the odds ratio estimates from the consistency and inconsistency models were compared.

Results

Search results: Of the 757 citations identified, 700 were excluded after examining their titles and abstracts and the full manuscripts of the remaining 57 were assessed. From those, we identified 8 systematic reviews.\textsuperscript{1,3,4,18-28} Figure 1 shows a modified PRISMA diagram describing the selection of studies. Of those reviews, 5 included a meta-analysis of the data. Six out of the 8 reviews were found to have met the following criteria: duplicate study selection and data extraction; comprehensive literature search; provided characteristics of their included studies; and assessed their included studies’ scientific quality. Characteristics of these reviews are described in Appendix 2 and their AMSTAR assessment is detailed in Appendix 3.

Description of included studies: Thirty randomized controlled trials\textsuperscript{29-58}, with a total of 10,193 patients, were then identified from the systematic reviews and included in the network meta-analysis. In most randomized controlled trials, a single telemedicine intervention was compared with usual care. For most studies (21 out of 30) patients mean age was greater than 65 and in all but one study the patients were mostly males. In 27 of 30 trials, participants were followed for 6 or more months and in 25 trials the intervention was delivered for 6 or more months.
However, the frequency of delivering the intervention did vary considerably. In most trials, the health professional that typically delivered the intervention was a nurse. A description of included trials is provided in Table 1.

**Quality assessment of included studies:** Using the SIGN-50 assessment tool we judged that 17 of the 30 randomized controlled trials were of high quality, 10 were acceptable and 3 were considered of poor quality. For the most part however, trials were judged to have appropriately randomized patients, adequately concealed allocation, similar groups at baseline, and had few losses to follow-up and analyzed patients according to the intention to treat. A summary of the quality of the trials is provided in Table 1 and further details on the assessment of trials using the SIGN-50 tool are provided in Appendix 4.

**Direct comparisons**

Twenty-nine trials contributed to the analysis of the outcome of death, twenty to the analysis of hospitalization and sixteen for the analysis of hospitalization due to heart failure. Of the 15 possible pairwise comparisons that can be made across the 6 interventions, the evidence available was found to have examined 8 comparisons directly for death as well as for hospitalization, and 6 for hospitalization due to heart failure. Figure 2 shows the evidence network for the outcome of death. For the outcomes of hospitalization and heart failure hospitalization, the evidence networks are provided in Appendix 5.

Direct comparisons (Figures 3-5) show that telemonitoring was found to be more effective than usual care in reducing the numbers of death (Odds ratio (OR) 0.52 95% Confidence Intervals (CI) [0.37, 0.72]), hospitalization (OR 0.70 95% CI [0.51, 0.96]), and hospitalization resulting from heart failure (OR 0.70 95% CI [0.51, 0.98]). Fewer patients receiving structured telephone
support interventions were hospitalized for all causes (OR 0.86 95% CI [0.77, 0.97]) and due to heart failure (OR 0.76 95% CI [0.65, 0.89]) than patients who received usual care. Similarly, fewer patients who received telemedicine interventions that involved the use of ECG data transmission were hospitalized than patients who received usual care (OR 0.70 CI [0.55, 0.91]). No other comparisons were found to suggest a significant benefit across the outcomes of death, hospitalization and heart failure related hospitalization for one intervention over the other. For all outcomes, heterogeneity was found to be either low or moderate. Forest plots of each pairwise meta-analysis conducted are made available in Appendix 6.

**Incorporation of data from the indirect comparisons of interventions**

*All-cause mortality:* Compared with usual care, the only interventions that significantly reduced the odds of death were structured telephone support [OR 0.7972 95% Credible Intervals (CrI) (0.6589, 0.9603)] and telemonitoring [OR 0.5312 95% CrI (0.3634, 0.7969)]. No other significant differences were observed across treatment comparisons (Figure 3). In terms of potentially reducing the odds of death, telemonitoring ranked first, followed by structured telephone support delivered in combination with telemonitoring, electrocardiographic data transmission, structured telephone support, usual care and video monitoring.

*Hospitalization:* For the most part, the odds of hospitalization did not significantly vary across interventions (Figure 4) making these results relatively consistent with the results from the direct pairwise analyses. The main difference however, was that in this analysis, both structured telephone support and telemonitoring were no longer found to significantly reduce all-cause hospitalization compared to usual care. However, these results are considered more
robust given their incorporation of all available data from both direct and indirect comparisons. According to their relative potential for reducing hospitalizations, telemonitoring was ranked first, followed by video monitoring, structured telephone support, electrocardiographic data transmission, usual care and structured telephone support and telemonitoring.

Heart failure hospitalization: The incorporation of indirect evidence confirmed that structured telephone support interventions [OR 0.6911 95% CrI (0.5621, 0.8462)], telemonitoring interventions [OR 0.6374 95% CrI (0.3932, 0.9479)] and telemedicine that included the transmission of electrocardiographic data [OR 0.7083 95% CrI (0.5161, 0.9805)] all significantly reduced hospitalizations due to heart failure compared to usual care. The remaining comparisons did not show favor for one intervention over the other (Figure 5). Once again, telemonitoring interventions ranked first, followed by structured telephone support, telemedicine that involved electrocardiographic data transmission, structured telephone support and telemonitoring interventions delivered together and usual care.

Examination of model fit and inconsistency: For the analysis of all outcomes, the consistency models had lower DIC values than the inconsistency models and residual deviances were comparable to the number of unconstrained data points. This indicated the goodness of fit of the selected models. Compared to the fixed effects models, the random effects models had lower residual deviance values and were therefore used to analyze all outcomes (Appendix 7). Across all outcomes the Brooks-Gelman-Rubin plots demonstrated model convergence (Appendix 8). Inconsistency was examined by plotting the deviances from the consistency model against the deviances from the inconsistency model for each outcome. There was little evidence of inconsistency from the plots (Appendix 9). The effect estimates were also
compared between models for treatment comparisons having direct evidence and were found to be similar across both models (Appendix 10).

**Subgroup analyses:** Compared to usual care, structured telephone support and telemonitoring interventions were found to significantly reduce deaths in studies where patients’ mean age was over 65. Subgroup analyses by age did not differ from the primary analysis of hospitalization in that no significant differences were found across interventions. For hospitalization due to heart failure, telemonitoring was the only intervention that showed significant improvement when compared to usual care for patients aged under the age of 65. On the other hand, structured telephone support was found to be significantly better than usual care in patients aged above 65 (Appendix 11).

**Sensitivity analyses:** To examine other potential sources of heterogeneity in the network, the following areas were examined across all included studies in subsequent sensitivity analyses: randomization, concealment of allocation, degree of loss to follow-up, and the inclusion of all randomized participants in the analysis according to the intention to treat principle. Studies were considered to be of high quality if they satisfied all of the aforementioned criteria. When trials that were judged to have a high risk of bias were excluded, the number of studies included in the analysis of death, hospitalization and hospitalization due to heart failure were reduced to 26, 16, and 14, respectively. For the most part, the estimates for all outcomes were consistent with the main analyses. There was one exception in that telemonitoring was no longer found to significantly reduce deaths compared to usual care [OR 0.635 95% CrI (0.3584, 1.121)] (Appendix 12).
Additional sensitivity analyses were conducted by repeating the primary analysis using a fixed-effect method. For all comparisons and across all outcomes, the results of both the fixed-effect and the random-effect model were consistent. Only on two occasions, the fixed-effect model showed a significant reduction where the random-effect model did not. According to the fixed-effect model, telemonitoring was associated with significantly lower odds of death compared to the structured telephone support intervention [OR 0.6451 95% CrI (0.4429, 0.9397)]. This reduction was not considered significant when a random-effect model was used [OR 0.6669 95% CrI [0.4361, 1.064)]. The same situation occurred when structured telephone support was compared to usual care for the outcome of all-cause hospitalization. The fixed-effect model estimate was found to be significant [OR 0.8647 95% CrI (0.7693, 0.972)] whereas the estimate from the random-effect model was not [OR 0.8796 95% CrI (0.7394, 1.063)]. Estimates from the fixed effects models are listed in Appendix 13.

**Interpretation**

Telemonitoring as well as structured telephone support interventions were both found to be significantly better than usual care in reducing deaths and heart failure related hospitalizations. Telemedicine interventions that involved the use of electrocardiographic (ECG) data transmission were also significantly more effective in reducing hospitalizations due to heart failure when compared with usual care. There were no other significant differences found across the interventions compared. As a further examination of the data, subgroup analyses were conducted and showed that, for the most part, telemonitoring interventions delivered alone continued to be the most effective across the three main outcomes. These findings were therefore considered to lend support to our main analysis and emphasize as well, the potential
advantage of this analysis as it was able to incorporate data from both indirect and direct comparisons.

Most of the evidence that is currently available on the impact of telemedicine interventions involves the comparison of an active form of telemedicine to standard care. As such, findings from this network meta-analysis are unique in that they examine the various comparisons across five main forms of active telemedicine interventions. For the first time, the currently available interventions were ranked according to their effectiveness in reducing the outcomes of death, hospitalization and hospitalization due to heart failure. When these different interventions were ranked, telemonitoring was always ranked first. These findings may help inform clinicians about which forms of telemedicine may be most effective in rehabilitating heart failure patients.

In a recent Cochrane review, Inglis (2011) found that telemonitoring was effective in reducing the risk of all-cause mortality but not structured telephone support interventions. Structured telephone support was also effective in reducing the risk of all-cause hospitalization in patients with chronic heart failure as was telemonitoring. Both these interventions were effective again in reducing the proportion of patients with a CHF-related hospitalization. Pairwise meta-analyses from this review were fairly consistent with the findings by Inglis (2011) as telemonitoring compared to usual care was also found to effectively reduce all outcomes and structured telephone support compared to usual care only significantly reduced all-cause hospitalizations and hospitalizations due to heart failure.
Consistent with the reviews by Inglis (2011) and Clarke (2011), when data from indirect comparisons were incorporated, telemonitoring compared to usual care continued to have a significant effect on reducing deaths.\textsuperscript{3,4} Unlike the findings by Inglis (2011) however, structured telephone support interventions were also found to significantly reduce deaths compared to usual care and no intervention was found to significantly reduce all-cause hospitalization.

Findings from this review were consistent to those from the review by Clarke (2011) which found no significant effect for telemonitoring compared to usual care for reducing all-cause hospital admissions.

For the outcome of hospitalizations due to heart failure, findings from this review were consistent once again with the findings by Inglis (2011). Both reviews found that both structured telephone support interventions and telemonitoring interventions were significantly more effective than usual care in reducing hospitalizations due to heart failure. Clarke (2011) also demonstrated a significant reduction in hospitalization due to heart failure for telemonitoring when compared to usual care.

This review demonstrated that the amount of evidence available in the literature for directly comparing across the active forms of telemedicine was limited. As such, the analysis of the comparisons across active telemedicine intervention relied mainly on indirect evidence. However, this allowed for the comparison of interventions that had not been previously compared in the literature and the integration of direct and indirect comparisons resulted in a gain of statistical precision compared with previous analyses.
This network analysis was limited to only including randomized controlled trials. This was deemed appropriate, however, given the availability of a substantial amount of evidence and the reduced likelihood of bias and confounding associated with this study design. As is the case with any meta-analysis, the quality of the analysis depends on the quality of the included data. For the most part, however, the risk of bias associated with included studies was found to be either low or acceptable and further sensitivity analyses did not significantly differ from the study’s main analysis.

Finally, the use of posterior probabilities may have resulted in a better understanding of what constitutes a clinically relevant reduction in odds of death or hospitalization. However, the absence of statistically robust evidence of a beneficial effect should not be confused with evidence of absence of benefit associated with telemedicine interventions.

Conclusion

This work represents the first application of network meta-analysis to combine data from randomized trials that examined the impact of telemedicine interventions on heart failure patient outcomes. Findings from this network meta-analysis are therefore considered to have greater precision given our incorporation of data from both direct and indirect evidence. This analysis has demonstrated that telemonitoring interventions were generally considered the most beneficial form of telemedicine for heart failure patients, and has also shown the potential positive effect that structured telephone support and telemonitoring interventions and may specifically have on the outcomes of death and hospitalization due to heart failure.
**Acknowledgements:** We thank Dr. Alaa Kotb for his thorough review of this report and thoughtful suggestions. The present study was supported by the Ontario Graduate Scholarship.

**Contributor of Authors:** AK and GW conceived and designed the meta-analysis. AK and SH identified and acquired selected reviews and trials, extracted the data, and conducted the quality assessment. AK, GW, and CC analyzed and interpreted the data. GW and CC provided statistical advice and input. AK, GW and CC contributed to the interpretation of the data. AK drafted the manuscript. GW, CC, SH, and HS critically reviewed the manuscript.

**Declaration of interest:** None declared.
References


4. Inglis S, Clark R, et al. (2011)"Structured telephone support or telemonitoring programmes for patients with chronic heart failure." Cochrane database of systematic reviews (Online) 8..


25. Inglis S, Clark R, et al. (2010) "A meta-analysis of 8,323 heart failure patients receiving structured telephone support or non-invasive telemonitoring to reduce
mortality, hospitalisation and cost.” European Journal of Heart Failure Supplements 9: S179


583-639.

Tables and figures

Records identified through database searching (n = 757)

Review of titles and abstracts

Records excluded (n = 700)

Full-text assessed (n = 57)

Records excluded (n = 43):
- 22 not systematic reviews of RCTs
- 9 were not specific to HF patients
- 6 not the targeted interventions
- 6 outcome data could not be extracted

14 citations describing 8 reviews meeting criteria

30 unique trials identified for the network meta-analysis

Figure 1: Flow chart for the identification of studies used in the network meta-analysis of telemedicine interventions for heart failure patients.
<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Study population</th>
<th>Interventions</th>
<th>Follow-up lengths</th>
<th>Sign-50</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angermann 2007</td>
<td>Chronic HF Patient age was 68 +/- 12 years, 29% were female, and 40% were in NYHA class III-IV.</td>
<td>Structured telephone support vs. Usual Care</td>
<td>6 months duration</td>
<td>Acceptable</td>
</tr>
<tr>
<td>Balk 2008</td>
<td>Median age was 66 years, 89% had systolic Left Ventricular dysfunction, and 90% were in NYHA class II or III.</td>
<td>Telemonitoring vs. Usual Care</td>
<td>mean follow-up duration of 9.6 months</td>
<td>High quality</td>
</tr>
<tr>
<td>Blum 2007</td>
<td>Age 72; 28% female and 46% were NYHA class III.</td>
<td>Telemonitoring including ECG data transmission vs. Usual care</td>
<td>Mean follow-up of 24 months</td>
<td>Acceptable</td>
</tr>
<tr>
<td>Capomolla 2004</td>
<td>Chronic HF; age 57; Male:Female ratio was 117/16; NYHA II/III-IV 89/44</td>
<td>Both Structured telephone support and Telemonitoring vs. Usual Care</td>
<td>12 months</td>
<td>High quality</td>
</tr>
<tr>
<td>Cleland 2005</td>
<td>48% were aged &gt; 70 years; NYHA class IV heart failure in the previous month, although 62% reported well-controlled symptoms (NYHA functional class I/II)</td>
<td>Telemonitoring including ECG data transmission vs. Structured telephone support vs. Usual care</td>
<td>8 months</td>
<td>High quality</td>
</tr>
<tr>
<td>De Lusignan 2001</td>
<td>Chronic HF aged 75, average NYHA 1.75</td>
<td>Video monitoring vs. Usual Care</td>
<td>12</td>
<td>Unacceptable</td>
</tr>
<tr>
<td>DeBusk 2004</td>
<td>mean age of patients was 72; 51% NYHA III or IV; 51% Male</td>
<td>Structured telephone support vs. Usual Care</td>
<td>12</td>
<td>High quality</td>
</tr>
<tr>
<td>Dendale 2012</td>
<td>Chronic HF; mean age 76; 65% male;</td>
<td>Telemonitoring vs. Usual Care</td>
<td>6</td>
<td>High quality</td>
</tr>
<tr>
<td>DeWalt 2006</td>
<td>Mean age 62; 58% male in intervention group and 41% in control; 40% in intervention were NYHA III and 51% in control</td>
<td>Structured telephone support vs. Usual Care</td>
<td>12</td>
<td>High quality</td>
</tr>
<tr>
<td>Study</td>
<td>Study Details</td>
<td>Intervention Comparison</td>
<td>Study Quality</td>
<td></td>
</tr>
<tr>
<td>------------------</td>
<td>-------------------------------------------------------------------------------</td>
<td>-----------------------------------------------------------------------------------------</td>
<td>---------------</td>
<td></td>
</tr>
<tr>
<td>Ekman 1998</td>
<td>Mean age 80; 42% females</td>
<td>Structured telephone support vs. Usual Care</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Galbreath 2004</td>
<td>Mean age 70.9; 29% female; 21% NYHA III</td>
<td>Structured telephone support vs. Usual Care</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>GESICA 2005</td>
<td>The mean age was 65 years, 71% were men, most patients were in NYHA class II or III</td>
<td>Structured telephone support vs. Usual Care</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Giordano 2009</td>
<td>Chronic HF; Aged 57; 16% female in Telemonitoring group and 14% in usual care; NYHA III-IV 46% in TM and 35% in UC</td>
<td>Telemonitoring vs. Usual Care</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Goldberg 2003</td>
<td>Mean age was 59 and 68% were male; 75% of NYHA III and 24% in NYHA IV</td>
<td>Telemonitoring vs. Usual Care</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Kielblock 2007</td>
<td>Chronic HF aged approx. 73, 42.6% female in I and 55.3% in Control</td>
<td>Telemonitoring vs. Usual Care</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Koehler 2011</td>
<td>Chronic HF; aged 67 n approx. 80% male; 50% NYHA III and 50% II</td>
<td>Telemonitoring including ECG data transmission vs. Usual care</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>Krum 2009</td>
<td>Chronic HF; aged 75; 65% male; 58.2% NYHA III and IV</td>
<td>Structured telephone support vs. Usual Care</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Krumholz 2002</td>
<td>HF and the median age of the patients was 74 years; 57% were men</td>
<td>Structured telephone support vs. Usual Care</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Laramee 2003</td>
<td>Mean age 70; 42% female in the Intervention group and 50% in Control</td>
<td>Structured telephone support vs. Usual Care</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Mortara 2009</td>
<td>Age 60; approx. 15% female</td>
<td>Structured telephone support vs. Both Structured telephone support and Telemonitoring vs. Usual Care</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Age/sex/Class</td>
<td>Intervention/Control</td>
<td>Study Type</td>
<td>Duration</td>
</tr>
<tr>
<td>---------------</td>
<td>--------------</td>
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<td>-------------------------------------</td>
<td>----------</td>
</tr>
<tr>
<td>Ramachandran 2007</td>
<td>Age 44; 22% Female; 74% NYHA I and II</td>
<td>Structured telephone support vs. Usual Care</td>
<td>6</td>
<td>Acceptable</td>
</tr>
<tr>
<td>Riegel 2002</td>
<td>Age 73, female 46% in the Intervention group and 54% in Control</td>
<td>Structured telephone support vs. Usual Care</td>
<td>6</td>
<td>Unacceptable</td>
</tr>
<tr>
<td>Riegel 2006</td>
<td>Age 72; 54% female; 81% NYHA III/IV</td>
<td>Structured telephone support vs. Usual Care</td>
<td>6</td>
<td>High quality</td>
</tr>
<tr>
<td>Schwarz 2008</td>
<td>Age 78; 43% female in the Intervention group and 61% in Usual Care</td>
<td>Telemonitoring to patients and their caregivers vs. Usual Care</td>
<td>3</td>
<td>High quality</td>
</tr>
<tr>
<td>Sisk 2006</td>
<td>Age 60; 47% females; approx. 45% NYHA IV</td>
<td>Structured telephone support vs. Usual Care</td>
<td>12</td>
<td>High quality</td>
</tr>
<tr>
<td>Villani 2007</td>
<td>Age 64 in Control group and 69 in the intervention group; 75% male</td>
<td>Telemonitoring including ECG data transmission vs. Usual care</td>
<td>12</td>
<td>Acceptable</td>
</tr>
<tr>
<td>Wade 2011</td>
<td>Approx. 76 age; 48% female</td>
<td>Telemonitoring + Case Management (CM) (calls/education) vs. CM (calls/education)</td>
<td>6</td>
<td>Acceptable</td>
</tr>
<tr>
<td>Wakefield 2008</td>
<td>Age 69; 99% male; 65% NYHA III</td>
<td>Video monitoring vs. Telephone support vs. Usual Care</td>
<td>12</td>
<td>High quality</td>
</tr>
<tr>
<td>Woodend 2008</td>
<td>Age 67; 72% male; approx. 62% NYHA III or higher</td>
<td>Video monitoring vs. Usual Care</td>
<td>12</td>
<td>High quality</td>
</tr>
<tr>
<td>Zugck 2008</td>
<td>Age 62; 85.5% male; 80% NYHA II</td>
<td>Telemonitoring vs. Usual Care</td>
<td>3</td>
<td>Acceptable</td>
</tr>
</tbody>
</table>
Figure 2: Evidence networks for interventions included in the analysis of death. Each node represents an intervention and the size of each node indicates how many patients received it of the total number of patients included in the network (N=10,193). The solid lines connecting the nodes together indicate the existence of this comparison of interventions in the literature. The thickness of the lines represents how many studies of the total number of studies (30 studies) include a particular comparison. UC = usual care. STS = structured telephone support. TM = telemonitoring. RPM = structured telephone support alongside telemonitoring. Video = video monitoring. ECG = telemedicine using electrocardiography.
### Figure 3: The impact of different forms of telemedicine on the outcome of death.

The odds ratios and 95% Credible Intervals for the comparisons in this diagram should be read from left to right (e.g. Patients receiving structured telephone support had an odds ratio of 0.80 [0.66, 0.96] reduced odds of death compared to those receiving usual care). Significant results are underlined and in bold.
<table>
<thead>
<tr>
<th>Comparison</th>
<th>Meta-analysis estimates</th>
<th>Network analysis estimates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Structured Telephone support</td>
<td>NA</td>
<td>0.98 [0.60, 1.61]</td>
</tr>
<tr>
<td>1.18 (0.73, 1.91) Telemonitoring</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>0.84 (0.56, 1.28) Telemonitoring &amp; Telephone support</td>
<td>0.71 (0.38, 1.33)</td>
<td>NA</td>
</tr>
<tr>
<td>1.10 (0.53, 2.25) Video monitoring</td>
<td>0.94 (0.40, 2.12)</td>
<td>1.32 (0.57, 2.96)</td>
</tr>
<tr>
<td>0.89 (0.64, 1.24) ECG monitoring</td>
<td>0.76 (0.44, 1.27)</td>
<td>1.06 (0.63, 1.78)</td>
</tr>
<tr>
<td>0.88 (0.74, 1.06) Usual Care</td>
<td>0.75 (0.48, 1.18)</td>
<td>1.052 (0.68, 1.63)</td>
</tr>
</tbody>
</table>

**Figure 4:** The impact of different forms of telemedicine on the outcome of hospitalization. Significant results are underlined and in bold.
<table>
<thead>
<tr>
<th>Comparison</th>
<th>Meta-analysis estimates</th>
<th>Network analysis estimates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Structured Telephone support</td>
<td>NA</td>
<td>0.74 [0.34, 1.62]</td>
</tr>
<tr>
<td>1.08 (0.70, 1.84)</td>
<td>Telemonitoring</td>
<td>NA</td>
</tr>
<tr>
<td>0.67 (0.34, 1.34)</td>
<td>0.62 (0.27, 1.35)</td>
<td>Telemonitoring &amp; Telephone support</td>
</tr>
<tr>
<td>0.98 (0.68, 1.40)</td>
<td>0.90 (0.50, 1.47)</td>
<td>1.46 (0.68, 3.01)</td>
</tr>
<tr>
<td>0.69 (0.56, 0.85)</td>
<td>0.64 (0.39, 0.95)</td>
<td>1.03 (0.53, 1.99)</td>
</tr>
</tbody>
</table>

**Figure 5: The impact of different forms of telemedicine on the outcome of heart failure.**

Significant results are underlined and in bold.
### Appendices

#### Appendix 1: Electronic search strategy

**Medline**

<table>
<thead>
<tr>
<th>Step</th>
<th>Query</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>telemedicine.mp.</td>
<td>(11504)</td>
</tr>
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30 CABG.mp. (11686)
31 exp Coronary Artery Bypass/ (42946)
32 coronary artery bypass.mp. (49943)
33 PCI.mp. (11200)
34 PTCA.mp. (6087)
35 exp Angioplasty, Balloon, Coronary/ (32274)
36 exp Coronary Artery Disease/ (33262)
37 coronary artery disease.mp. (74636)
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44 cardiac failure.mp. (9616)
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46 angina.mp. or exp Angina, Stable/ or exp Angina Pectoris/ or exp Angina, Unstable/ (62861)
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48 22 and 47 (1822)
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52 Meta-Analysis/ (38678)
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54 exp Review Literature as Topic/ (6684)
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56 cochrane.ab. (24378)
57 embase.ab. (22086)
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(psychinfo or psycinfo).ab. (8479)
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bids.ab. (339)
cancerlit.ab. (568)
56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 (40020)
reference list$.ab. (8427)
bibliograph$.ab. (10669)
hand-search$.ab. (3464)
relevant journals.ab. (619)
manual search$.ab. (2014)
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selection criteria.ab. (17698)
data extraction.ab. (8577)
71 or 72 (24850)
Review/ (1770613)
73 or 74 (1778932)
Comment/ (528661)
Letter/ (786831)
Editorial/ (323802)
animal/ (5114599)
human/ (12764478)
79 not (79 and 80) (3731794)
or/76-78,81 (4911854)
55 or 64 or 70 or 75 (1836799)
83 not 82 (1676453)
48 and 84 (183)

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1  telemmedicine.mp. or exp telemedicine/ or exp telecommunication/ (33029)
2  telecommunication.mp. (16756)
reminder systems.mp. or exp reminder system/ (1540)
telehealth.mp. or exp telehealth/ (16787)
home monitoring.mp. or exp home monitoring/ (3388)
"home monitor*".mp. (3488)
telecardiology.mp. or exp teleconsultation/ or exp telecardiology/ or exp telemetry/ (19056)
exp teleradiology/ or teleradiology.mp. (1523)
"remot* monitor*".mp. (1075)
"telemonitor*".mp. (1074)
television support.mp. (442)
Speech Recognition Software.mp. or exp automatic speech recognition/ (518)
exp interactive voice response system/ or interactive voice response.mp. (550)
telemetry.mp. (14066)
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heart failure.mp. or exp heart failure/ (307863)
coronary disease.mp. or exp coronary artery disease/ (218972)
coronary artery disease.mp. (173166)
(coronary adj2 disease).ab.ti. (137077)
myocardial infarction.mp. or exp heart infarction/ (293858)
heart infarction.mp. (254831)
exp coronary artery bypass graft/ or CABG.mp. (56812)
coronary artery bypass.mp. (67715)
exp percutaneous coronary intervention/ or PCI.mp. (60159)
percutaneous coronary intervention.mp. or exp transluminal coronary angioplasty/ (54419)
exp percutaneous transluminal angioplasty balloon/ or exp angioplasty/ or exp percutaneous transluminal angioplasty/ or angioplasty.mp. (75926)
heart attack.mp. (3796)
cardiac arrest.mp. or exp heart arrest/ (50240)
cardiac failure.mp. or exp heart failure/ (283371)
angina.mp. or exp angina pectoris/ (96405)
ischemic heart disease.mp. or exp ischemic heart disease/ (470464)
acute coronary syndrome.mp. or exp acute coronary syndrome/ (25722)
acs.mp. (15431)
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35 exp Meta Analysis/ (67825)
36 ((meta adj analy$) or metaanalys$).tw. (63259)
37 (systematic adj (review$1 or overview$1)).tw. (48992)
38 35 or 36 or 37 (125392)
39 cancerlit.ab. (667)
40 cochrane.ab. (28842)
41 embase.ab. (25782)
42 (psychlit or psyclit).ab. (957)
43 (psychinfo or psycinfo).ab. (6385)
44 (cinahl or cinhal).ab. (8749)
45 science citation index.ab. (1915)
46 bids.ab. (436)
47 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 (44036)
48 reference lists.ab. (8639)
49 bibliograph$.ab. (17743)
50 hand-search$.ab. (3980)
51 manual search$.ab. (2283)
52 relevant journals.ab. (724)
53 48 or 49 or 50 or 51 or 52 (30491)
54 data extraction.ab. (10629)
55 selection criteria.ab. (19478)
56 54 or 55 (28750)
57 review.pt. (1919616)
58 56 or 57 (1931280)
59 letter.pt. (807623)
60 editorial.pt. (421593)
61 animal/ (1810429)
62 human/ (14108254)
63 61 not (61 and 62) (1354958)
64 or/59-60,63 (2570545)
The Cochrane Library
1 telemedicine.mp. [mp=title, short title, abstract, full text, keywords, caption text] (46)
2 telehealth.mp. [mp=title, short title, abstract, full text, keywords, caption text] (21)
3 telecommunication.mp. [mp=title, short title, abstract, full text, keywords, caption text] (23)
4 reminder systems.mp. [mp=title, short title, abstract, full text, keywords, caption text] (37)
5 "home monitor**".mp. [mp=title, short title, abstract, full text, keywords, caption text] (16)
6 telecardiology.mp. [mp=title, short title, abstract, full text, keywords, caption text] (1)
7 teleradiology.mp. [mp=title, short title, abstract, full text, keywords, caption text] (3)
8 "remot* monitor**".mp. [mp=title, short title, abstract, full text, keywords, caption text] (4)
9 "telemonitor**".mp. [mp=title, short title, abstract, full text, keywords, caption text] (8)
10 telephone support.mp. [mp=title, short title, abstract, full text, keywords, caption text] (37)
11 Speech Recognition Software.mp. [mp=title, short title, abstract, full text, keywords, caption text] (1)
12 reminder systems.mp. [mp=title, short title, abstract, full text, keywords, caption text] (37)
13 telemetry.mp. [mp=title, short title, abstract, full text, keywords, caption text] (9)
14 voice response.mp. [mp=title, short title, abstract, full text, keywords, caption text] (54)
15 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 (188)
16 heart failure.mp. [mp=title, short title, abstract, full text, keywords, caption text] (495)
17 coronary disease.mp. [mp=title, short title, abstract, full text, keywords, caption text] (99)
18 (coronary adj2 disease).mp. [mp=title, short title, abstract, full text, keywords, caption text] (383)
19 myocardial infarction.mp. [mp=title, short title, abstract, full text, keywords, caption text] (652)
20 CABG.mp. [mp=title, short title, abstract, full text, keywords, caption text] (79)
21 PCI.mp. [mp=title, short title, abstract, full text, keywords, caption text] (43)
22 PTCA.mp. [mp=title, short title, abstract, full text, keywords, caption text] (35)
23 coronary artery bypass.mp. [mp=title, short title, abstract, full text, keywords, caption text] (106)
24 angioplasty.mp. [mp=title, short title, abstract, full text, keywords, caption text] (120)
25 balloon.mp. [mp=title, short title, abstract, full text, keywords, caption text] (152)
26 coronary artery disease.mp. [mp=title, short title, abstract, full text, keywords, caption text] (173)
heart attack.mp. [mp=title, short title, abstract, full text, keywords, caption text] (98)

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angina.mp. [mp=title, short title, abstract, full text, keywords, caption text] (276)

16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 (1352)

15 and 35 (61)
Appendix 2: Characteristics of included reviews

Table 2: Description of included systematic reviews

<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Included studies</th>
<th>Patients</th>
<th>Intervention/Comparison</th>
<th>Outcomes</th>
<th>Main findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chaudhry 2007</td>
<td>9 studies (sample range 134-1518)</td>
<td>Adult heart failure patients only</td>
<td>I: regular nurse delivered telephone calls over 6-12+ months to monitor symptoms; I: twice daily monitoring of symptoms and weight for 6 months; I: for 3 months daily monitoring of weight blood pressure HR and oxygen saturation compared with home nurse visits; I: physiologic monitoring consisting of twice daily self-measurements and monthly calls by nurse to assess symptoms and meds; I: video conferencing with integrated stethoscope and nurse telephone support; C: usual care</td>
<td>All-cause hospitalizations; HF-hospitalization; Mortality; Cost</td>
<td>The evidence base for telemonitoring in heart failure is currently quite limited. Based on the available data, telemonitoring may be an effective strategy for disease management in high-risk heart failure patients.</td>
</tr>
<tr>
<td>Clark 2007</td>
<td>14 studies (ranged from 161-1518)</td>
<td>CHF patients at home</td>
<td>Structured telephone support: included monitoring of symptoms medicine management and education and counseling on life-style. Telemonitoring: included transfer of daily data on weight pulse blood pressure and</td>
<td>Primary: Mortality, admission, CHF admission; Secondary: HRQOL cost and applicability</td>
<td>Programs for chronic heart failure that include remote monitoring have a positive effect on clinical outcomes in community dwelling patients with chronic heart failure.</td>
</tr>
<tr>
<td>Study (Year)</td>
<td>Type of Study</td>
<td>Intervention Details</td>
<td>Outcomes Evaluated</td>
<td>Summary</td>
<td></td>
</tr>
<tr>
<td>-------------------</td>
<td>---------------</td>
<td>--------------------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------------------------------------</td>
<td>---------</td>
<td></td>
</tr>
<tr>
<td>Clarke 2011</td>
<td>13 studies</td>
<td>Congestive HF at home</td>
<td>Telemonitoring (no telephone only intervention; Collected data on signs, symptoms and physiologic measurement)</td>
<td>All-cause mortality, CHF admission, emergency admission, length of stay medication adherence and cost.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(57-461 sample range)</td>
<td></td>
<td></td>
<td>Telemonitoring in conjunction with nurse home visiting and specialist unit support can be effective in the clinical management of patients with CHF and help to improve their quality of life.</td>
<td></td>
</tr>
<tr>
<td>Dang 2009</td>
<td>9 studies</td>
<td>Congestive HF</td>
<td>Automated monitoring or automated physiologic monitoring; excluded telephone-only monitoring interventions</td>
<td>Overall admissions, HF admissions, mortality, healthcare utilization costs</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(37-461 sample range)</td>
<td></td>
<td></td>
<td>Available data suggest that telemonitoring is a promising strategy. More data are needed to determine the ideal patient population technology and parameters frequency and duration of telemonitoring and the exact combination of case management and close monitoring that would assure consistent and improved outcomes with cost reductions in HF.</td>
<td></td>
</tr>
<tr>
<td>Giamouzis 2012</td>
<td>12 studies</td>
<td>Chronic HF</td>
<td>Telemonitoring measuring physiological parameter vs. usual care</td>
<td>Cost, all-cause mortality, hospitalization</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(57-710 sample range)</td>
<td></td>
<td></td>
<td>Nevertheless, it appears that the above presented randomized controlled trials tend to be in favor of telemonitoring.</td>
<td></td>
</tr>
<tr>
<td>Holland 2004</td>
<td>3 (553 sample)</td>
<td>HF</td>
<td>Videophone or any form of home physiological monitoring (group B) vs. usual care</td>
<td>All-cause hospital admission, all-cause mortality, and heart failure hospital admission</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Multidisciplinary interventions for heart failure reduce both hospital admission and all-cause mortality. The most effective interventions were delivered at least partly in the home</td>
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<tr>
<td>Inglis 2011 [including]</td>
<td>29 studies</td>
<td>CHF</td>
<td>TM and Structured TF delivered by health</td>
<td>All-cause mortality, CHF</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Structured telephone support and</td>
<td></td>
</tr>
<tr>
<td>Abstracts Clark S100; Clark 944-945; Inglis S179; Inglis 1028-1040; Inglis S90; Inglis 878</td>
<td>(sample 8323)</td>
<td>Professionals for discharged patients who are not also getting intensified follow up or home visits vs. usual care</td>
<td>Related hospitalization, all-cause readmissions, length of stay, QOL, acceptability and healthcare cost savings</td>
<td>Telemonitoring are effective in reducing the risk of all-cause mortality and CHF-related hospitalizations in patients with CHF; they improve quality of life, reduce costs, and evidence-based prescribing.</td>
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<td></td>
</tr>
<tr>
<td>Klersy 2011</td>
<td>21 studies (sample = 5715)</td>
<td>HF</td>
<td>Remote patient monitoring (regular structured telephone or electronic transfer of physiological data) vs. usual care</td>
<td>Cost analysis using hospitalization and length of stay outcomes</td>
<td>The novel cost-effectiveness data coupled with the demonstrated clinical efficacy of RPM should encourage its acceptance Amongst clinicians and its consideration by third-party payers. At the same time, the scientific community should acknowledge the lack of prospectively and uniformly collected economic data and should request that future studies incorporate economic analyses.</td>
</tr>
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</table>
### Table 3: Summary of the AMSTAR Assessment

<table>
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<th>Study</th>
<th>AMSTAR Criteria</th>
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<td>Can’t answer</td>
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<tr>
<td>Clark 2007</td>
<td>Can’t answer</td>
</tr>
<tr>
<td>Clarke 2011</td>
<td>Can’t answer</td>
</tr>
<tr>
<td>Dang 2009</td>
<td>Can’t answer</td>
</tr>
<tr>
<td>Giamouzis 2012</td>
<td>Can’t answer</td>
</tr>
<tr>
<td>Holland 2013</td>
<td>Can’t answer</td>
</tr>
<tr>
<td>Inglis 2011</td>
<td>Can’t answer</td>
</tr>
<tr>
<td>Klersy 2009 (and</td>
<td>Can’t answer</td>
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<td>Klersy 2010)</td>
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</table>

**Note:** NA=Not applicable. (1) Was an ‘a priori’ design provided? (2) Was there duplicate study selection and data extraction? (3) Was a comprehensive literature search performed? (4) Was the status of publication (i.e. grey literature) used as an inclusion criterion? (5) Was a list of studies (included and excluded) provided? (6) Were the characteristics of the included studies provided? (7) Was the scientific quality of the included studies assessed and documented? (8) Was the scientific quality of the included studies used appropriately in formulating conclusions? (9) Were the methods used to combine the findings of studies appropriate? (10) Was the likelihood of publication bias assessed? (11) Was the conflict of interest included?
Appendix 4: Quality assessment of included trials

Table 4: Summary of the SIGN-50 assessment

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<td>Capomolla 2004</td>
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<tr>
<td>Cleland 2005</td>
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</tr>
<tr>
<td>De Lusignan 2001</td>
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<td>DeBusk 2004</td>
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<td>Dendale 2012</td>
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<td>DeWalt 2006</td>
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<td>Ekman 1998</td>
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<td>Galbreath 2004</td>
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<td>GESICA 2005</td>
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<td>Giordano 2009</td>
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<td>Goldberg 2003</td>
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<td>Study</td>
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<td>Kielblock 2007</td>
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<td>Koehler 2011</td>
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<td>Yes</td>
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<td>Krumholz 2002</td>
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<td>Laramee 2003</td>
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<td>Mortara 2009</td>
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<td>Ramachandran 2007</td>
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<td>Riegel 2002</td>
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<td>Schwarz 2008</td>
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<td>Sisk 2006</td>
<td>Yes</td>
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<td>Villani 2007</td>
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<td>Wade 2011</td>
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<td>Woodend 2008</td>
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### Zugck 2005

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<th>Can’t say</th>
<th>Can’t say</th>
<th>Yes</th>
<th>Can’t say</th>
<th>Can’t say</th>
<th>NA</th>
<th>+</th>
</tr>
</thead>
</table>

**Note:** NA=Not applicable. High quality (++) Acceptable (+) Unacceptable (0).

1.1 The study addresses an appropriate and clearly focused question. 1.2 The assignment of subjects to treatment groups is randomized. 1.3 An adequate concealment method is used. 1.4 Subjects and investigators are kept ‘blind’ about treatment allocation. 1.5 The treatment and control groups are similar at the start of the trial. 1.6 The only difference between groups is the treatment under investigation. 1.7 All relevant outcomes are measured in a standard, valid and reliable way. 1.8 What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed? 1.9 All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention to treat analysis). 1.10 Where the study is carried out at more than one site, results are comparable for all sites. 2.1 How well was the study done to minimise bias?
Appendix 5: Evidence networks for all-cause hospitalization and heart failure hospitalization.

Figure 6: Evidence networks for interventions included in the analysis of all-cause hospitalization. UC = usual care. STS = structured telephone support. TM = telemonitoring. RPM = structured telephone support alongside telemonitoring. Video = video monitoring. ECG = telemedicine using electrocardiography.
Figure 7: Evidence networks for interventions included in the analysis of heart failure hospitalization. UC = usual care. STS = structured telephone support. TM = telemonitoring. RPM = structured telephone support alongside telemonitoring. ECG = telemedicine using electrocardiography.
Appendix 6: Summary of the direct pairwise comparisons

### Death

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Trials</th>
<th>OR (95% CI)</th>
<th>(I^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VIDEO vs UC</td>
<td>3</td>
<td>1.20 (0.61, 2.37)</td>
<td>0%</td>
</tr>
<tr>
<td>TM vs UC</td>
<td>6</td>
<td>0.52 (0.37, 0.72)</td>
<td>19.3%</td>
</tr>
<tr>
<td>STS vs VIDEO</td>
<td>1</td>
<td>0.67 (0.27, 1.67)</td>
<td>NA</td>
</tr>
<tr>
<td>STS vs UC</td>
<td>15</td>
<td>0.85 [0.73, 1.00]</td>
<td>13.2%</td>
</tr>
<tr>
<td>STS vs STS &amp; TM</td>
<td>1</td>
<td>1.11 (0.47, 2.64)</td>
<td>NA</td>
</tr>
<tr>
<td>STS vs ECG</td>
<td>1</td>
<td>0.93 (0.55, 1.57)</td>
<td>NA</td>
</tr>
<tr>
<td>STS &amp; TM vs UC</td>
<td>3</td>
<td>0.79 (0.55, 1.14)</td>
<td>0%</td>
</tr>
<tr>
<td>ECG vs UC</td>
<td>4</td>
<td>0.83 (0.63, 1.08)</td>
<td>3.8%</td>
</tr>
</tbody>
</table>

### Hospitalization

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Trials</th>
<th>OR (95% CI)</th>
<th>(I^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>STS vs UC</td>
<td>12</td>
<td>0.86 [0.77, 0.97]</td>
<td>7.9%</td>
</tr>
<tr>
<td>TM vs UC</td>
<td>3</td>
<td>0.70 [0.51, 0.96]</td>
<td>0%</td>
</tr>
<tr>
<td>STS &amp; TM vs UC</td>
<td>1</td>
<td>1.28 [0.82, 2.00]</td>
<td>NA</td>
</tr>
<tr>
<td>VIDEO vs UC</td>
<td>2</td>
<td>0.74 [0.40, 1.35]</td>
<td>71.7%</td>
</tr>
<tr>
<td>ECG vs UC</td>
<td>4</td>
<td>0.99 [0.81, 1.20]</td>
<td>77.5%</td>
</tr>
<tr>
<td>STS vs ECG</td>
<td>1</td>
<td>0.91 [0.59, 1.39]</td>
<td>NA</td>
</tr>
<tr>
<td>STS vs VIDEO</td>
<td>1</td>
<td>1.09 [0.49, 2.44]</td>
<td>NA</td>
</tr>
<tr>
<td>STS vs STS &amp; TM</td>
<td>1</td>
<td>0.98 [0.60, 1.61]</td>
<td>NA</td>
</tr>
</tbody>
</table>

### HF-Hospitalization

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Trials</th>
<th>OR (95% CI)</th>
<th>(I^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECG vs UC</td>
<td>3</td>
<td>0.70 [0.55, 0.91]</td>
<td>43.7%</td>
</tr>
<tr>
<td>STS &amp; TM vs UC</td>
<td>1</td>
<td>1.11 [0.58, 2.12]</td>
<td>NA</td>
</tr>
<tr>
<td>STS vs ECG</td>
<td>1</td>
<td>0.78 [0.46, 1.32]</td>
<td>NA</td>
</tr>
<tr>
<td>STS vs STS &amp; TM</td>
<td>1</td>
<td>0.74 [0.34, 1.62]</td>
<td>NA</td>
</tr>
<tr>
<td>STS vs UC</td>
<td>11</td>
<td>0.76 [0.65, 0.89]</td>
<td>0%</td>
</tr>
<tr>
<td>TM vs UC</td>
<td>3</td>
<td>0.70 [0.51, 0.98]</td>
<td>45.5%</td>
</tr>
</tbody>
</table>

Figure 8: Estimates of odds ratios for pairwise comparisons between usual care (UC) structured telephone support (STS), telemedicine, video monitoring (Video) and telemedicine involving ECG (ECG).
Appendix 7: Comparison across models for each outcome.

Table 5: DIC and Residual Deviances across different models for each outcome

<table>
<thead>
<tr>
<th>Outcome: death</th>
<th>Random Effects Model</th>
<th>Fixed Effects Model</th>
<th>Inconsistency Model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Datapoints</td>
<td>61</td>
<td>61</td>
<td>61</td>
</tr>
<tr>
<td>Residual deviance</td>
<td>56.96</td>
<td>60.74</td>
<td>58.54</td>
</tr>
<tr>
<td>DIC</td>
<td>358.341</td>
<td>357.422</td>
<td>360.763</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcome: hospitalization</th>
<th>Random Effects Model</th>
<th>Fixed Effects Model</th>
<th>Inconsistency Model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Datapoints</td>
<td>43</td>
<td>43</td>
<td>43</td>
</tr>
<tr>
<td>Residual deviance</td>
<td>45.84</td>
<td>55.61</td>
<td>46.41</td>
</tr>
<tr>
<td>DIC</td>
<td>302.364</td>
<td>304.619</td>
<td>303.922</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcome: Heart failure hospitalization</th>
<th>Random Effects Model</th>
<th>Fixed Effects Model</th>
<th>Inconsistency Model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Datapoints</td>
<td>34</td>
<td>34</td>
<td>34</td>
</tr>
<tr>
<td>Residual deviance</td>
<td><strong>33.32</strong></td>
<td>35.41</td>
<td>33.36</td>
</tr>
<tr>
<td>DIC</td>
<td>223.202</td>
<td>221.678</td>
<td>223.096</td>
</tr>
</tbody>
</table>
Appendix 8: Gelman Rubin plots

Figure 9: Gelman Rubin plots for the outcome of death. The convergence of the model is seen when the Gelman-Rubin statistic (shown as the red line) approaches 1.
Figure 10: Gelman Rubin plots for the outcome of Hospitalization. The convergence of the model is seen when the Gelman-Rubin statistic (shown as the red line) approaches 1.
Figure 11: Gelman Rubin plots for the outcome HF-Hospitalization. The convergence of the model is seen when the Gelman-Rubin statistic (shown as the red line) approaches 1.
Appendix 9: Inconsistency plots

Figure 12: Inconsistency plot for the outcome of Death

Figure 13: Inconsistency plot for the outcome of Hospitalization
Figure 14: Inconsistency plot for the outcome of Hospitalization due to heart failure
Appendix 10: Comparing direct evidence between models.

Table 6: Comparing direct evidence between models for the outcome of Death

<table>
<thead>
<tr>
<th>node</th>
<th>OR-Consistency model</th>
<th>OR-Inconsistency model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2.50%</td>
<td>median</td>
</tr>
<tr>
<td>or[Usual Care, Structured telephone support]</td>
<td>0.6589</td>
<td>0.7972</td>
</tr>
<tr>
<td>or[Usual Care, Telemonitoring]</td>
<td>0.3634</td>
<td>0.5312</td>
</tr>
<tr>
<td>or[Usual Care, Structured telephone support plus Telemonitoring]</td>
<td>0.5082</td>
<td>0.7664</td>
</tr>
<tr>
<td>or[Usual Care, Video monitoring]</td>
<td>0.5845</td>
<td>1.176</td>
</tr>
<tr>
<td>or[Usual Care, ECG monitoring]</td>
<td>0.5665</td>
<td>0.7838</td>
</tr>
<tr>
<td>or[Structured telephone support, Structured telephone support plus Telemonitoring]</td>
<td>0.6262</td>
<td>0.9615</td>
</tr>
</tbody>
</table>
Table 7: Comparing direct evidence between models for the outcome of Hospitalization

<table>
<thead>
<tr>
<th>Node</th>
<th>OR-Consistency model</th>
<th>OR-Inconsistency model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2.50%</td>
<td>median</td>
</tr>
<tr>
<td>or[Usual Care, Structured telephone support]</td>
<td>0.7394</td>
<td>0.8796</td>
</tr>
<tr>
<td>or[Usual Care, Telemonitoring]</td>
<td>0.4781</td>
<td>0.7471</td>
</tr>
<tr>
<td>or[Usual Care, Structured telephone support plus Telemonitoring]</td>
<td>0.6818</td>
<td>1.052</td>
</tr>
<tr>
<td>or[Usual Care, Video monitoring]</td>
<td>0.3946</td>
<td>0.7981</td>
</tr>
<tr>
<td>or[Usual Care, ECG monitoring]</td>
<td>0.7419</td>
<td>0.9883</td>
</tr>
<tr>
<td>or[Structured telephone support, Structured telephone support plus Telemonitoring]</td>
<td>0.7816</td>
<td>1.196</td>
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</table>
Table 8: Comparing direct evidence between models for the outcome of HF-Hospitalization

<table>
<thead>
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<th>Node</th>
<th>OR-Consistency model</th>
<th>OR-Inconsistency model</th>
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<tbody>
<tr>
<td></td>
<td>2.50%</td>
<td>median</td>
</tr>
<tr>
<td>or[Usual Care, Structured telephone support]</td>
<td>0.5621</td>
<td>0.6911</td>
</tr>
<tr>
<td>or[Usual Care, Telemonitoring]</td>
<td>0.3932</td>
<td>0.6374</td>
</tr>
<tr>
<td>or[Usual Care, Structured telephone support plus Telemonitoring]</td>
<td>0.5256</td>
<td>1.034</td>
</tr>
<tr>
<td>or[Usual Care, ECG monitoring]</td>
<td>0.5161</td>
<td>0.7083</td>
</tr>
</tbody>
</table>
Appendix 11: Subgroup analysis

Table 9: Subgroup analysis, according to age group, for the outcome of death.

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Main analysis</th>
<th></th>
<th></th>
<th></th>
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<th></th>
<th></th>
<th></th>
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<th></th>
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<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>OR [Credible intervals]</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>2.50%</td>
<td>median</td>
<td>97.50%</td>
<td>2.50%</td>
<td>median</td>
<td>97.50%</td>
<td>2.50%</td>
<td>median</td>
<td>97.50%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>or[UC,STS]</td>
<td>0.6589</td>
<td>0.7972</td>
<td>0.9603</td>
<td>0.468</td>
<td>0.8482</td>
<td>1.464</td>
<td>0.6012</td>
<td>0.7677</td>
<td>0.9935</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>or[UC,TM]</td>
<td>0.3634</td>
<td>0.5312</td>
<td>0.7969</td>
<td>0.2382</td>
<td>0.8778</td>
<td>3.391</td>
<td>0.3185</td>
<td>0.5022</td>
<td>0.7877</td>
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<td></td>
</tr>
<tr>
<td>or[UC,RPM]</td>
<td>0.5082</td>
<td>0.7664</td>
<td>1.154</td>
<td>0.3458</td>
<td>0.9211</td>
<td>2.292</td>
<td>0.4041</td>
<td>0.6861</td>
<td>1.174</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>or[UC,Video]</td>
<td>0.5845</td>
<td>1.176</td>
<td>2.345</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>0.5858</td>
<td>1.178</td>
<td>2.309</td>
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<tr>
<td>or[UC,ECG]</td>
<td>0.5665</td>
<td>0.7838</td>
<td>1.064</td>
<td>0.1848</td>
<td>0.6166</td>
<td>2.041</td>
<td>0.565</td>
<td>0.8275</td>
<td>1.179</td>
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<tr>
<td>or[STS,TM]</td>
<td>0.4361</td>
<td>0.6669</td>
<td>1.047</td>
<td>0.2584</td>
<td>1.041</td>
<td>4.569</td>
<td>0.3905</td>
<td>0.6539</td>
<td>1.095</td>
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<tr>
<td>or[STS,RPM]</td>
<td>0.6262</td>
<td>0.9615</td>
<td>1.484</td>
<td>0.3908</td>
<td>1.092</td>
<td>2.937</td>
<td>0.5056</td>
<td>0.8953</td>
<td>1.574</td>
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<tr>
<td>or[STS,Video]</td>
<td>0.7196</td>
<td>1.476</td>
<td>2.975</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>0.7504</td>
<td>1.537</td>
<td>3.051</td>
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<tr>
<td>or[STS,ECG]</td>
<td>0.6878</td>
<td>0.9827</td>
<td>1.385</td>
<td>0.1967</td>
<td>0.7272</td>
<td>2.798</td>
<td>0.7033</td>
<td>1.079</td>
<td>1.604</td>
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</tr>
<tr>
<td>or[TM,RPM]</td>
<td>0.8142</td>
<td>1.434</td>
<td>2.546</td>
<td>0.1964</td>
<td>1.053</td>
<td>5.071</td>
<td>0.6776</td>
<td>1.37</td>
<td>2.743</td>
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<tr>
<td>or[TM,Video]</td>
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<td>NA</td>
<td>NA</td>
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<td>5.301</td>
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<tr>
<td>or[TM,ECG]</td>
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<td>1.476</td>
<td>2.394</td>
<td>0.1153</td>
<td>0.7031</td>
<td>3.947</td>
<td>0.9122</td>
<td>1.649</td>
<td>2.934</td>
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<tr>
<td>or[RPM,Video]</td>
<td>0.6847</td>
<td>1.542</td>
<td>3.445</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>0.7173</td>
<td>1.722</td>
<td>4.04</td>
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<tr>
<td>or[RPM,ECG]</td>
<td>0.6069</td>
<td>1.021</td>
<td>1.703</td>
<td>0.1511</td>
<td>0.668</td>
<td>3.149</td>
<td>0.6277</td>
<td>1.201</td>
<td>2.285</td>
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<tr>
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<td>0.6672</td>
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<td>NA</td>
<td>NA</td>
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<td>0.6983</td>
<td>1.541</td>
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</tbody>
</table>

Note: STS = structured telephone support. TM = telemonitoring. RPM = structured telephone support alongside telemonitoring. Video = video monitoring. ECG = telemedicine using electrocardiography. Significant findings are in bold and underlined.
### Table 10: Subgroup analysis, according to age group, for the outcome of hospitalization.

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Main analysis OR [Credible intervals]</th>
<th>Under 65 OR [Credible intervals]</th>
<th>Above 65 OR [Credible intervals]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2.50%</td>
<td>median</td>
<td>97.50%</td>
</tr>
<tr>
<td>or[UC,STS]</td>
<td>0.7394</td>
<td>0.8796</td>
<td>1.063</td>
</tr>
<tr>
<td>or[UC,TM]</td>
<td>0.4781</td>
<td>0.7471</td>
<td>1.165</td>
</tr>
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<td>or[UC,RPM]</td>
<td>0.6818</td>
<td>1.052</td>
<td>1.626</td>
</tr>
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<td>or[UC,Video]</td>
<td>0.3946</td>
<td>0.7981</td>
<td>1.645</td>
</tr>
<tr>
<td>or[UC,ECG]</td>
<td>0.7419</td>
<td>0.9883</td>
<td>1.337</td>
</tr>
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<td>or[STS,TM]</td>
<td>0.5232</td>
<td>0.8489</td>
<td>1.362</td>
</tr>
<tr>
<td>or[STS,RPM]</td>
<td>0.7816</td>
<td>1.196</td>
<td>1.81</td>
</tr>
<tr>
<td>or[STS,Video]</td>
<td>0.4454</td>
<td>0.9071</td>
<td>1.872</td>
</tr>
<tr>
<td>or[STS,ECG]</td>
<td>0.8098</td>
<td>1.123</td>
<td>1.565</td>
</tr>
<tr>
<td>or[TM,RPM]</td>
<td>0.7528</td>
<td>1.409</td>
<td>2.62</td>
</tr>
<tr>
<td>or[TM,Video]</td>
<td>0.4719</td>
<td>1.064</td>
<td>2.525</td>
</tr>
<tr>
<td>or[TM,ECG]</td>
<td>0.7856</td>
<td>1.321</td>
<td>2.267</td>
</tr>
<tr>
<td>or[RPM,Video]</td>
<td>0.3378</td>
<td>0.7574</td>
<td>1.758</td>
</tr>
<tr>
<td>or[RPM,ECG]</td>
<td>0.5624</td>
<td>0.9399</td>
<td>1.581</td>
</tr>
<tr>
<td>or[Video,ECG]</td>
<td>0.5671</td>
<td>1.239</td>
<td>2.639</td>
</tr>
</tbody>
</table>

Note: STS = structured telephone support. TM = telemonitoring. RPM = structured telephone support alongside telemonitoring. Video = video monitoring. ECG = telemedicine using electrocardiography. Significant findings are in bold and underlined.
Table 11: Subgroup analysis, according to age group, for the outcome of heart failure hospitalization.

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Main analysis OR [Credible intervals]</th>
<th>Under 65 OR [Credible intervals]</th>
<th>Above 65 OR [Credible intervals]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2.50% median 97.50%</td>
<td>2.50% median 97.50%</td>
<td>2.50% median 97.50%</td>
</tr>
<tr>
<td>or[UC,STS]</td>
<td>0.5621 0.6911 0.8462</td>
<td>0.4529 0.7256 1.344</td>
<td>0.513 0.6833 0.9004</td>
</tr>
<tr>
<td>or[UC,TM]</td>
<td>0.3932 0.6374 0.9479</td>
<td>0.145 0.3642 0.9198</td>
<td>0.4492 0.8142 1.458</td>
</tr>
<tr>
<td>or[UC,RPM]</td>
<td>0.5256 1.034 1.99</td>
<td>0.4134 1.058 2.851</td>
<td>NA NA NA</td>
</tr>
<tr>
<td>or[UC,ECG]</td>
<td>0.5161 0.7083 0.9805</td>
<td>0.1868 0.4932 1.289</td>
<td>0.5457 0.8388 1.281</td>
</tr>
<tr>
<td>or[STS,TM]</td>
<td>0.545 0.9238 1.426</td>
<td>0.1644 0.4994 1.399</td>
<td>0.6275 1.189 2.289</td>
</tr>
<tr>
<td>or[STS,RPM]</td>
<td>0.7466 1.497 2.922</td>
<td>0.524 1.447 3.754</td>
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</tr>
<tr>
<td>or[STS,ECG]</td>
<td>0.7155 1.026 1.481</td>
<td>0.2052 0.6774 1.906</td>
<td>0.7735 1.227 1.955</td>
</tr>
<tr>
<td>or[TM,RPM]</td>
<td>0.7389 1.622 3.686</td>
<td>0.7905 2.895 11.11</td>
<td>NA NA NA</td>
</tr>
<tr>
<td>or[TM,ECG]</td>
<td>0.6818 1.11 2.009</td>
<td>0.3575 1.353 5.048</td>
<td>0.4986 1.032 2.119</td>
</tr>
<tr>
<td>or[RPM,ECG]</td>
<td>0.3323 0.6835 1.469</td>
<td>0.1152 0.4674 1.755</td>
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</tr>
</tbody>
</table>

Note: STS = structured telephone support. TM = telemonitoring. RPM = structured telephone support alongside telemonitoring. ECG = telemedicine using electrocardiography. Significant findings are in bold and underlined.
Appendix 12: Sensitivity analysis results

Table 12: Sensitivity analysis excluding studies with low quality, according to SIGN-50, for the outcome of death.

<table>
<thead>
<tr>
<th>Primary analysis</th>
<th>OR [Credible intervals]</th>
<th>Sign 50 (-) excluded</th>
<th>OR [Credible intervals]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2.50%</td>
<td>50%</td>
<td>2.50%</td>
</tr>
<tr>
<td></td>
<td>median</td>
<td>97.50%</td>
<td>median</td>
</tr>
<tr>
<td>or[UC,STS]</td>
<td>0.6589 0.7972 0.9603</td>
<td>or[UC,STS] 0.6475 0.7937 0.9672</td>
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</tr>
<tr>
<td>or[UC,TM]</td>
<td>0.3634 0.5312 0.7969</td>
<td>or[UC,TM] 0.3584 0.635 1.121</td>
<td></td>
</tr>
<tr>
<td>or[UC,RPM]</td>
<td>0.5082 0.7664 1.154</td>
<td>or[UC,RPM] 0.5031 0.7579 1.162</td>
<td></td>
</tr>
<tr>
<td>or[UC,Video]</td>
<td>0.5845 1.176 2.345</td>
<td>or[UC,Video] 0.6077 1.281 2.647</td>
<td></td>
</tr>
<tr>
<td>or[UC,ECG]</td>
<td>0.5665 0.7838 1.064</td>
<td>or[UC,ECG] 0.5592 0.7818 1.068</td>
<td></td>
</tr>
<tr>
<td>or[STS,TM]</td>
<td>0.4361 0.6669 1.047</td>
<td>or[STS,TM] 0.4324 0.8028 1.467</td>
<td></td>
</tr>
<tr>
<td>or[STS,RPM]</td>
<td>0.6262 0.9615 1.484</td>
<td>or[STS,RPM] 0.62 0.9573 1.497</td>
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<tr>
<td>or[STS,Video]</td>
<td>0.7196 1.476 2.975</td>
<td>or[STS,Video] 0.7521 1.617 3.361</td>
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<tr>
<td>or[STS,ECG]</td>
<td>0.6878 0.9827 1.385</td>
<td>or[STS,ECG] 0.6812 0.9855 1.401</td>
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<tr>
<td>or[TM,RPM]</td>
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<td>or[TM,RPM] 0.5827 1.197 2.442</td>
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<tr>
<td>or[TM,Video]</td>
<td>0.994 2.212 4.929</td>
<td>or[TM,Video] 0.7817 2.013 5.11</td>
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<tr>
<td>or[TM,ECG]</td>
<td>0.8717 1.476 2.394</td>
<td>or[TM,ECG] 0.6287 1.229 2.359</td>
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<tr>
<td>or[RPM,Video]</td>
<td>0.6847 1.542 3.445</td>
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<tr>
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<tr>
<td>or[Video,ECG]</td>
<td>0.3144 0.6672 1.42</td>
<td>or[Video,ECG] 0.2739 0.6087 1.359</td>
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</table>

Note: STS = structured telephone support. TM = telemonitoring. RPM = structured telephone support alongside telemonitoring. Video = video monitoring. ECG = telemedicine using electrocardiography. The main difference observed is in bold and underlined.
Table 13: Sensitivity analysis excluding studies with low quality, according to SIGN-50, for the outcome of hospitalization.

<table>
<thead>
<tr>
<th>Primary analysis</th>
<th>OR [Credible intervals]</th>
<th>Sign 50 (-) excluded</th>
<th>OR [Credible intervals]</th>
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</thead>
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<tr>
<td></td>
<td>2.50%</td>
<td>median</td>
<td>97.50%</td>
</tr>
<tr>
<td>or[UC,STS]</td>
<td>0.7394</td>
<td>0.8796</td>
<td>1.063</td>
</tr>
<tr>
<td>or[UC,TM]</td>
<td>0.4781</td>
<td>0.7471</td>
<td>1.165</td>
</tr>
<tr>
<td>or[UC,RPM]</td>
<td>0.6818</td>
<td>1.052</td>
<td>1.626</td>
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<td>or[UC,Video]</td>
<td>0.3946</td>
<td>0.7981</td>
<td>1.645</td>
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<td>or[UC,ECG]</td>
<td>0.7419</td>
<td>0.9883</td>
<td>1.337</td>
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<tr>
<td>or[STS,TM]</td>
<td>0.5232</td>
<td>0.8489</td>
<td>1.362</td>
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<tr>
<td>or[STS,RPM]</td>
<td>0.7816</td>
<td>1.196</td>
<td>1.81</td>
</tr>
<tr>
<td>or[STS,Video]</td>
<td>0.4454</td>
<td>0.9071</td>
<td>1.872</td>
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<td>or[STS,ECG]</td>
<td>0.8098</td>
<td>1.123</td>
<td>1.565</td>
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<tr>
<td>or[TM,RPM]</td>
<td>0.7528</td>
<td>1.409</td>
<td>2.62</td>
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<tr>
<td>or[TM,Video]</td>
<td>0.4719</td>
<td>1.064</td>
<td>2.525</td>
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<td>or[TM,ECG]</td>
<td>0.7856</td>
<td>1.321</td>
<td>2.267</td>
</tr>
<tr>
<td>or[RPM,Video]</td>
<td>0.3378</td>
<td>0.7574</td>
<td>1.758</td>
</tr>
<tr>
<td>or[RPM,ECG]</td>
<td>0.5624</td>
<td>0.9399</td>
<td>1.581</td>
</tr>
<tr>
<td>or[Video,ECG]</td>
<td>0.5671</td>
<td>1.239</td>
<td>2.639</td>
</tr>
</tbody>
</table>

Note: STS = structured telephone support. TM = telemonitoring. RPM = structured telephone support alongside telemonitoring. Video = video monitoring. ECG = telemedicine using electrocardiography.
Table 14: Sensitivity analysis excluding studies with low quality, according to SIGN-50, for the outcome of heart failure hospitalization.

<table>
<thead>
<tr>
<th>Primary analysis</th>
<th>OR [Credible intervals]</th>
<th>Sign 50 (-) excluded</th>
<th>OR [Credible intervals]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2.50% median 97.50%</td>
<td></td>
<td>2.50% median 97.50%</td>
</tr>
<tr>
<td>or[UC,STS]</td>
<td>0.5621 0.6911 0.8462</td>
<td>or[UC,STS]</td>
<td>0.5683 0.7065 0.8708</td>
</tr>
<tr>
<td>or[UC,TM]</td>
<td>0.3932 0.6374 0.9479</td>
<td>or[UC,TM]</td>
<td>0.1732 0.365 0.7511</td>
</tr>
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<td>or[UC,RPM]</td>
<td>0.5256 1.034 1.99</td>
<td>or[UC,RPM]</td>
<td>0.5374 1.051 2.06</td>
</tr>
<tr>
<td>or[UC,ECG]</td>
<td>0.5161 0.7083 0.9805</td>
<td>or[UC,ECG]</td>
<td>0.518 0.7137 0.9758</td>
</tr>
<tr>
<td>or[STS,TM]</td>
<td>0.545 0.9238 1.426</td>
<td>or[STS,TM]</td>
<td>0.2403 0.5196 1.091</td>
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<tr>
<td>or[STS,RPM]</td>
<td>0.7466 1.497 2.922</td>
<td>or[STS,RPM]</td>
<td>0.7559 1.495 2.96</td>
</tr>
<tr>
<td>or[STS,ECG]</td>
<td>0.7155 1.026 1.481</td>
<td>or[STS,ECG]</td>
<td>0.7055 1.012 1.442</td>
</tr>
<tr>
<td>or[TM,RPM]</td>
<td>0.7389 1.622 3.686</td>
<td>or[TM,RPM]</td>
<td>1.068 2.868 7.806</td>
</tr>
<tr>
<td>or[TM,ECG]</td>
<td>0.6818 1.11 2.009</td>
<td>or[TM,ECG]</td>
<td>0.896 1.949 4.375</td>
</tr>
<tr>
<td>or[RPM,ECG]</td>
<td>0.3323 0.6835 1.469</td>
<td>or[RPM,ECG]</td>
<td>0.3243 0.6795 1.418</td>
</tr>
</tbody>
</table>

Note: STS = structured telephone support. TM = telemonitoring. RPM = structured telephone support alongside telemonitoring. ECG = telemedicine using electrocardiography.
**Appendix 13: Network meta-analysis results of fixed effects model**

**Table 15: Direct and indirect comparisons for death**

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Odds ratios (97.5% Credible intervals)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Usual care vs. structured telephone support</td>
<td>0.81 (0.69, 0.94)</td>
</tr>
<tr>
<td>Usual care vs. Telemonitoring</td>
<td>0.52 (0.37, 0.73)</td>
</tr>
<tr>
<td>Usual care vs. structured telephone support and Telemonitoring</td>
<td>0.75 (0.53, 1.01)</td>
</tr>
<tr>
<td>Usual care vs. telemedicine involving video monitoring</td>
<td>1.19 (0.62, 2.28)</td>
</tr>
<tr>
<td>Usual care vs. telemedicine involving electrocardiographic data transmission</td>
<td>0.80 (0.62, 1.03)</td>
</tr>
<tr>
<td>Structured telephone support vs. Telemonitoring</td>
<td>0.65 (0.44, 0.94)</td>
</tr>
<tr>
<td>Structured telephone support vs. structured telephone support and Telemonitoring</td>
<td>0.94 (0.65, 1.35)</td>
</tr>
<tr>
<td>Structured telephone support vs. telemedicine involving video monitoring</td>
<td>1.47 (0.77, 2.84)</td>
</tr>
<tr>
<td>Structured telephone support vs. telemedicine involving electrocardiographic data transmission</td>
<td>0.99 (0.75, 1.31)</td>
</tr>
<tr>
<td>Telemonitoring vs. structured telephone support and Telemonitoring</td>
<td>1.45 (0.89, 2.35)</td>
</tr>
<tr>
<td>Telemonitoring vs. telemedicine involving video monitoring</td>
<td>2.28 (1.09, 4.77)</td>
</tr>
<tr>
<td>Telemonitoring vs. telemedicine involving electrocardiographic data transmission</td>
<td>1.54 (1.005, 2.35)</td>
</tr>
<tr>
<td>Structured telephone support and Telemonitoring vs. video monitoring</td>
<td>1.58 (0.76, 3.28)</td>
</tr>
<tr>
<td>Structured telephone support and Telemonitoring vs. telemedicine involving electrocardiographic data transmission</td>
<td>1.06 (0.69, 1.63)</td>
</tr>
<tr>
<td>Video monitoring vs. telemedicine involving electrocardiographic data transmission</td>
<td>0.67 (0.34, 1.35)</td>
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### Table 16: Direct and indirect comparisons for hospitalization

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Odds ratios (97.5% Credible intervals)</th>
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</thead>
<tbody>
<tr>
<td>Usual care vs. structured telephone support</td>
<td>0.86 (0.77, 0.97)</td>
</tr>
<tr>
<td>Usual care vs. Telemonitoring</td>
<td>0.73 (0.53, 1.01)</td>
</tr>
<tr>
<td>Usual care vs. structured telephone support and Telemonitoring</td>
<td>1.05 (0.77, 1.43)</td>
</tr>
<tr>
<td>Usual care vs. telemedicine involving video monitoring</td>
<td>0.77 (0.41, 1.44)</td>
</tr>
<tr>
<td>Usual care vs. telemedicine involving electrocardiographic data transmission</td>
<td>0.98 (0.81, 1.19)</td>
</tr>
<tr>
<td>Structured telephone support vs. Telemonitoring</td>
<td>0.85 (0.60, 1.20)</td>
</tr>
<tr>
<td>Structured telephone support vs. structured telephone support and Telemonitoring</td>
<td>1.21 (0.89, 1.64)</td>
</tr>
<tr>
<td>Structured telephone support vs. telemedicine involving video monitoring</td>
<td>0.89 (0.47, 1.67)</td>
</tr>
<tr>
<td>Structured telephone support vs. telemedicine involving electrocardiographic data transmission</td>
<td>1.13 (0.92, 1.41)</td>
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<td>Telemonitoring vs. structured telephone support and telemedicine</td>
<td>1.42 (0.91, 2.23)</td>
</tr>
<tr>
<td>Telemonitoring vs. telemedicine involving video monitoring</td>
<td>1.04 (0.51, 2.12)</td>
</tr>
<tr>
<td>Telemonitoring vs. telemedicine involving electrocardiographic data transmission</td>
<td>1.34 (0.92, 1.94)</td>
</tr>
<tr>
<td>Structured telephone support and Telemonitoring vs. telemedicine involving video monitoring</td>
<td>0.73 (0.37, 1.47)</td>
</tr>
<tr>
<td>Structured telephone support and Telemonitoring vs. telemedicine involving electrocardiographic data transmission</td>
<td>0.94 (0.65, 1.35)</td>
</tr>
<tr>
<td>Telemedicine involving Video monitoring vs. telemedicine involving electrocardiographic data transmission</td>
<td>1.28 (0.66, 2.47)</td>
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</table>
### Table 17: Direct and indirect comparisons for HF-hospitalization

<table>
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<tr>
<th>Comparison</th>
<th>Odds ratios (97.5% Credible intervals)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Usual care vs. structured telephone support</td>
<td>0.69 (0.59, 0.81)</td>
</tr>
<tr>
<td>Usual care vs. Telemonitoring</td>
<td>0.67 (0.48, 0.94)</td>
</tr>
<tr>
<td>Usual care vs. structured telephone support and Telemonitoring</td>
<td>1.04 (0.58, 1.87)</td>
</tr>
<tr>
<td>Usual care vs. telemedicine involving electrocardiographic data transmission</td>
<td>0.71 (0.56, 0.91)</td>
</tr>
<tr>
<td>Structured telephone support vs. Telemonitoring</td>
<td>0.97 (0.67, 1.41)</td>
</tr>
<tr>
<td>Structured telephone support vs. structured telephone support and Telemonitoring</td>
<td>1.51 (0.83, 2.72)</td>
</tr>
<tr>
<td>Structured telephone support vs. telemedicine involving electrocardiographic data transmission</td>
<td>1.03 (0.78, 1.35)</td>
</tr>
<tr>
<td>Telemonitoring vs. structured telephone support and Telemonitoring</td>
<td>1.55 (0.79, 3.03)</td>
</tr>
<tr>
<td>Telemedicine vs. telemedicine involving electrocardiographic data transmission</td>
<td>1.06 (0.70, 1.60)</td>
</tr>
<tr>
<td>Structured telephone support and Telemonitoring vs. telemedicine involving electrocardiographic data transmission</td>
<td>0.68 (0.36, 1.29)</td>
</tr>
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</table>
CHAPTER FIVE: DESIGN OF A RANDOMIZED CONTROLLED TRIAL

The previous manuscripts addressed a gap in the literature regarding the specific impact of structured telephone support compared to usual care and the effectiveness of various forms of telemedicine compared to one another, respectively. The following is a manuscript prepared for publication, based on a design of a randomized controlled trial that aims to determine the impact of telemonitoring administered alongside structured telephone support on outcomes compared to telemonitoring alone during the cardiac rehabilitation of coronary artery disease patients with advanced heart failure.

This protocol follows the guidelines proposed by the Canadian Institute for Health Research for the development of randomized controlled trials. A copy of the framework adopted for the design of this trial is provided in Appendix D of the thesis.

This manuscript was co-authored by the student (AK) and his supervisor, Dr. George A. Wells. The student is first author of this paper, having been primarily responsible for the conception and design of the study and the writing of the manuscript. Dr. Wells provided guidance and valuable feedback throughout the process.
Helping Everyone Acquire Regular Treatment: A Randomized Controlled Trial to Evaluate a New Telemedicine Intervention for Heart Failure Patients

The Tele-HEART Trial

Study Protocol

Version 1.0

Dated August 30th 2013
SPONSOR:
Ottawa Heart Institute Research Corporation (OHIRC)
40 Ruskin Street
Ottawa Ontario
K1Y 4W7

CENTRAL COORDINATING CENTRE:
The Cardiovascular Research Method Centre (CRMC) at the University of Ottawa Heart Institute
40 Ruskin Street
Ottawa Ontario
K1Y 4W7
613-761-5442

PRINCIPAL INVESTIGATORS:
Ahmed Kotb
Clinical Researcher, Ottawa Heart Institute
40 Ruskin Street, Ottawa Ontario

Dr. George Wells MSc, PhD
Director Cardiovascular Research Methods Centre
U. of Ottawa Heart Institute
40 Ruskin Street Ottawa
K1Y 4W7 Canada

Heather Sherrard
Vice President of Clinical Services
U. of Ottawa Heart Institute
40 Ruskin Street Ottawa
K1Y 4W7 Canada
**Signatures:**

**Investigator Agreement**

“I have read this protocol and agree to abide by all provisions set forth therein. I agree to comply with the International Conference on Harmonisation Tripartite Guideline on Good Clinical Practice.”

<table>
<thead>
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<th>Investigator Signature</th>
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</thead>
<tbody>
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</table>
1. The Need for a Trial

1.1 Background

Cardiovascular diseases (CVD) are the leading cause of death worldwide. The World Health Organization (WHO) estimated that 17.5 million people died from CVD in 2005. At the time, this represented approximately 30% of the world’s mortality.\(^1\) In the past decade, the prevalence of CVD increased by 18.2%.\(^2\) In order to reduce the burden caused by CVD, effective primary and secondary prevention of these diseases is crucial.

Among the more common forms of heart diseases is coronary artery disease (CAD). CAD is one of the most common forms of heart disease that results from an impedance or blockage of one or more arteries that supply blood to the heart.\(^3\) Patients who have CAD may progress to having Heart Failure (HF) which is a complex debilitating syndrome that results from a cardiac dysfunction that impairs the ability of the ventricle to fill with or eject blood.\(^4\) As their heart disease is more advanced, these patients generally require increased levels monitoring and more intensive plans of care.

Cardiac rehabilitation (CR) is offered to individuals after cardiac events to aid recovery and reduce the likelihood of further cardiac illness. CR programs have been previously shown to improve physical health as well as decrease subsequent morbidity and mortality\(^5,6\) through exercise, education, behavior change, counseling and other strategies aimed at targeting traditional risk factors for cardiovascular disease.\(^7-10\) Despite these benefits however, patient participation in CR programs remains suboptimal. Only 15-30% of patients requiring rehabilitation are actually participating in rehabilitation programs. Some of the main reasons people give for not taking part in cardiac rehabilitation are difficulties in regularly attending
sessions and reluctance to take part in group-based classes. The degree of emphasis the treating physician places on the patient’s participation in cardiac rehabilitation and whether or not the physician is a cardiologist are both important predictors.

Patient adherence to rehabilitation is an additional concern. It is estimated that between 40% and 60% of people do not take medication as prescribed because of forgetfulness, changing medication schedules or busy lifestyles. Medications unused and/or returned to pharmacists are estimated to cost £100 million per annum in the United Kingdom. In the United States, the annual cost of illness due to non-adherence has been reckoned at US $100 billion.

To improve adherence, Osterberg identified the following four approaches: patient education; improved dosing schedules; increased access to health care; and improved communication between physicians and patients. Some evidence suggests as well that interventions involving motivational communications delivered through letters, telephone calls and home visits may be effective in increasing the uptake of cardiac rehabilitation. This offers promise as the provision of high quality care to a rapidly expanding population of older patients with chronic heart conditions becomes increasingly difficult. Specialist cardiovascular clinics are available only to a minority of patients and do not have the capacity for frequent patient review. On the other hand as well, patients may be unwilling or unable to make frequent clinic attendance due to financial, transport or disability constraints. For instance factors such as being younger, male, able to drive and having the perception that, prior to the cardiac event, the patient was
considered to be healthy are found to be associated with the highest participation and compliance rates.

As a result, many studies have recently sought to examine whether or not interventions that aim to facilitate the provision of specialized care to a large number of patients who may otherwise not access healthcare services could be effective and in which patient populations would they be most beneficial. These interventions are commonly known to as “Telemedicine”. One of the more commonly studied forms of telemedicine is known as “Telemonitoring”. It is defined as “the use of audio, video, and other telecommunications and electronic information processing technologies to monitor patient status at a distance.”. As such, telemonitoring often involves the transmission of biologic or physiologic data from one location to another for data interpretation and decision-making.

1.2 Current evidence

Earlier systematic reviews such as those by Louis in 2003 and Chaudhry in 2007 concluded that telemonitoring might have an important role in the delivery of health care for patients with heart failure but that the evidence was still limited. Telemonitoring is a form of telemedicine that typically involves the transmission of information on symptoms and signs between a healthcare professional and the patient. In 2007, a systematic review and meta-analysis of randomized controlled trials found that remote monitoring programs for patients with heart failure reduced HF-related admissions to hospital and all-cause mortality by nearly one fifth while improving health related quality of life, but had no significant effect on all cause admission to hospital. Similarly, in 2010 a systematic review by CADTH, found that home
telemonitoring of heart failure patients reduced mortality and hospitalizations compared to usual care. Additionally, they found that patient quality of life and satisfaction with home telemonitoring were similar or better than with usual care.\textsuperscript{26} In 2011, a systematic review and meta-analysis of randomized controlled trials comparing telemonitoring to usual care found that telemonitoring reduced all-cause mortality and hospital admissions resulting from heart failure but had no effect on overall hospital admissions, length of stay, medication adherence or cost.\textsuperscript{27} The general conclusion however, was that telemonitoring alone was insufficient to reduce readmission rates and improve quality of life, and must be integrated with nurse visits and specialist follow-up. As the benefit of telemedicine seemed to be consistently proven, studies began to examine whether these systems were cost-effective. A systematic review comparing the cost of telemonitoring and usual care concluded that although heart failure telemonitoring would require an initial financial investment, it would substantially reduce costs in the long term particularly by reducing re-hospitalization and travel costs.\textsuperscript{28}

Despite these promising findings however, it is important to note that the aforementioned reviews have examined very diverse telemedicine interventions. Not only did the interventions differ in their intensity, duration and frequency of administration from one review to the next but also within the included studies of each review. The comparator was, in most cases, considered “standard” or “usual” care however, this definition also varied significantly between studies. These clinical differences could therefore cause difficulties in combining and comparing results. Several reviews included trials that tested multifaceted approaches (multidisciplinary input, home/clinic visits, telephone support). As a consequence, it has been difficult to identify the benefits of the unique components of each intervention.
This became the focus of a recent Cochrane review. In this review, Inglis included trials examining the impact of standard telephone or more advanced telemonitoring technology systems (e.g. electronic transfer of physiological data – electrocardiograph (ECG), blood pressure (BP), weight, pulse oximetry, respiratory rate and medicine administration) if they were delivered to patients with HF living in the community as the only aftercare intervention, without home visits or intensified clinic follow-up. The interventions were found to reduce the rate of death from any cause by 44% and the rate of heart-failure-related hospitalizations by 21%.²⁹

These earlier results were later challenged by a large multi-center randomized controlled trial of 1653 HF patients. The study by Chaudhry found no reduction in the risk of readmission or death from any cause with telemonitoring as compared with usual care. There were also no reductions in the risk of hospitalization for heart failure, the number of days in the hospital, or the time to readmission or death. Moreover, subgroup analyses failed to identify a group for which the intervention was effective.³⁰

1.3 Scientific rationale for current study

The need for a study to guide clinicians considering telemedicine in the management of HF patients is evident for the following reasons:

- **HF is recognized to be a major health issue.** Suboptimal participation in cardiac rehabilitation and a lack of regular follow-up can result in further cardiac illness, increased rates of preventable hospital readmissions, deaths and overall burden to the health care system.
• **Inconsistency in available evidence regarding the usefulness of telemonitoring.** The result from a meta-analysis is often times similar to the result from the largest randomized controlled trial. In this case however, previous systematic reviews and meta-analyses produced very positive results for telemedicine \(^{25-27,29}\) whereas the large multicenter trial by Chaudhry showed no effect.\(^{30}\) On the one hand, the meta-analyses adopted very broad definitions of telemedicine that incorporated interventions that varied considerably across studies. They also varied in their standards of care included studies that have been small and underpowered. On the other hand, the previous trial by Chaudhry only followed patients for 6 months which may be insufficient to detect an effect on clinical events like deaths and rehospitalizations.

• **The lack of direct comparisons across different telemedicine interventions.** Most studies have compared some form of telemedicine to usual care and very few have studied how these active technologies compared against one another. With this lack of direct comparisons, we conducted a multiple-treatments meta-analysis of different currently available forms of telemedicine for heart failure patients. The results suggested that telemonitoring would be most effective in reducing both death and hospitalization due to heart failure.

• **The emergence of another effective form of telemedicine.** Structured telephone support (STS) is another commonly used form of telemedicine. In the context of cardiac rehabilitation, this involves regularly contacting patients to assess their overall health, status, their experience of symptoms, adherence to medication and their overall progress following discharge. In individuals with heart failure, a recent Cochrane review
found that STS interventions could significantly reduce heart failure hospitalizations compared to usual care. To date however, it remains unclear if this more basic intervention could be effective in reducing hospitalization and death in HF patients compared to the more complex telemonitoring intervention.

1.4 Research hypothesis

Telemonitoring delivered alongside structured telephone support, as compared to telemonitoring alone, will reduce all-cause mortality and hospitalization for coronary artery disease patients with heart failure (HF).

1.5 Research objectives

1.5.1 Primary

To determine if, in patients with HF, telemonitoring (TM) delivered in combination with structured telephone support (STS), compared to telemonitoring alone, will reduce all-cause mortality and heart failure hospitalization.

1.5.2 Secondary

The secondary objectives are to determine in patients with HF:

1) To determine if the intervention combining both STS and TM (TM+), compared to TM alone, reduces all-cause mortality, all-cause hospitalizations defined as an admission to a health care facility for > 24 hours, cardiovascular hospitalization or hospitalizations for heart failure.

2) To determine if TM+, compared to TM, provides greater control over risk factors like smoking, poor adherence to medication, systolic blood pressure, or low-density lipoprotein levels.
3) To determine if the TM+ intervention improves patients’ quality of life and exercise capacity compared to TM alone.

4) To determine the impact of TM+ compared with TM on all-cause mortality and hospitalization for heart failure according to sex (males vs. females) and age group (≤65 and >65 years of age).

5) To determine if the TM+ interventions causes greater anxiety for patients as a result of increased patient monitoring and involvement in their own care.

1.6 Benefits

Currently, the evidence around the effectiveness of structured telephone support for rehabilitating CAD patients has been limited. In the case of telemonitoring, although the evidence is not limited, it has been highly variable inconsistent. In previous reviews, the clinical differences that exist across included studies have made it difficult to reliably combine and compare results. This has also made it difficult to truly determine the potential benefits of each unique form of telemedicine and how they compare against each other. The result of this study will have a direct impact on the management of HF patients after their discharge. If telemonitoring alone (TM) were superior to telemonitoring plus structured telephone support (TM+) then TM would be optimal for the post-discharge care of HF patients and these results will provide needed support to the previously conducted network meta-analysis. On the other hand, if TM+ were superior to TM, then this option would be considered as the current most effective form of telemedicine in this population. This will have a profound impact on the understanding of telemedicine interventions in cardiac rehabilitation, how they compare
against one another as opposed to standard care, and on whether or not they should be considered as the new standard for post-discharge care for HF patients.

1.7 Risks
There are currently no data on the risk posed by the use of telemedicine in cardiac rehabilitation. However, it is important to consider the possibility that the increased patient monitoring and involvement of patients in their own care as a result of these interventions may cause feelings of anxiety. This risk will be monitored and compiled by Data Safety & Monitoring Committee that will consist of a HF specialist, a biostatistician with trial expertise and a scientist with extensive experience in cardiac rehabilitation.

1.8 Summary of background and rationale
Cardiac rehabilitation (CR) is effective in reducing further illness in patients with HF.

Recognizing 1) participation rates in CR programs remains suboptimal, 2) the potential usefulness of telemedicine in providing specialized cardiac care to a large number remotely, 3) the lack of consistent and reliable evidence regarding the effectiveness of telemonitoring and structured telephone support in improving cardiac risk factor control, morbidity and mortality for HF patients, clinicians are faced with the dilemma of recommending telemedicine interventions for their rehabilitating HF patients. Therefore the time is right to conduct a trial to compare the current best telemedicine intervention, telemonitoring, versus a new and promising intervention, telemonitoring plus structured telephone support, in patients with HF.
2. The Proposed Trial

2.1 Design

This is a phase 3, multi-centre prospective randomized open study with blinded endpoint assessment (i.e. PROBE design). The study flow diagram can be found in Appendix A and a detailed study schedule of events can be found in Appendix B.

2.1.1 Screening/Consent

Prior to randomization, all patients must have been receiving optimal medical therapy for heart failure patients with impaired LV function as per the 2013 ACCF/AHA guideline for the management of Heart Failure.

At each participating site, Research Ethics Board (REB) approvals will be obtained. Cardiologists and internists will be asked to give permission for their patients to be identified and enrolled. HF care managers (1 per site) would then identify potential participants and, while making daily rounds, inform potential participants about the study and gain oral permission for the Primary Investigator (PI) to contact them before their discharge. The PI would explain the study to the patient and/or caregiver, provide a letter of explanation and receive oral consent for a chart review and a point-of-care blood test (NT-proBNP) to verify if they meet study criteria. Patients will be asked to provide their phone numbers for contact upon discharge and will then be randomized. Details on the consent procedure are provided in Section 3.6.2.
2.2 Interventions

This trial will compare two forms of telemedicine interventions for patients with HF. The two arms of the study are 1) telemonitoring plus structured telephone support (TM+ group) and 2) telemonitoring alone (TM group).

2.2.1 Telemonitoring (TM)

At an initial home visit made to patients in both arms patients will receive advice on self-monitoring of HF, the health monitor connected to the electronic weight scale and BP monitoring device will be installed and patients will be taught how to use it. During the six months following their discharge, patients will be trained to transmit their daily vital signs and weight measurements. Participants’ training will include practice sessions and the provision of a detailed user manual, diary, together with standardized study forms for measuring and transmitting vital signs. All participants’ measurements will be taken at a fixed hour in the morning according to a standardized protocol. The health monitor will also automatically generate supplementary questions directly to the patient to evaluate worsening HF symptoms, medication, exercise, and smoking status. When on two consecutive days no measurements were received by the central computer, a frequency alert will be generated. Patients will be called by phone to stimulate them to make the recordings or to help them in the case of malfunction.

The data collected will be stored in a database that will alert the nurses to respond when a potential problem is flagged. Prespecified alert limits are determined for the following measurements:

- Body weight (plus or minus 2 kg from discharge body weight)
• Systolic Blood Pressure (SBP) 140mmHg upper limit and 90mmHg lower limit
• Heart Rate (HR) upper limit 90bpm and lower limit 50bpm.

When recordings fall outside of these limits for 2 consecutive days, the GP and HF clinic will be alerted by automatic email containing a graph of the evolution of the parameter that caused the alert. At that moment, per protocol the GP will contact the patient and adapt the treatment if he/she feels necessary. The HF nurse will contact the patient by telephone 1-3 days after the alert to verify whether the intervention was effective.

As part of the Ontario Telemedicine Network (OTN), all participating centres have had prior experience in offering a range of telemedicine services through programs such as the Telemedicine Local Health Integration Network (LHIN) Nurse program and the Telehome care program. The Telemedicine LHIN Nurse program brings together one hundred and ninety-one full time nurses across their fourteen member sites. The Telehomecare program nurses teach, coach and remotely monitor a patient’s health status using telemedicine. The nurses involved in the trial will also receive training as far as filling out the patients’ personal health record, use of telemedicine equipment and interpretation of the patient’s vital sign data trend. Additional training and technical support for the participating centres, will be made available to them by the coordinator center throughout the trial using remote assistance with occasional on-site support.

2.2.2 Telemonitoring and Structured Telephone Support (TM+)

Participants allocated to receive the new intervention will receive the same TM intervention in addition to biweekly STS monitoring. The STS intervention will be delivered using interactive
voice response technology, an automated speech recognition calling system. For the six months following discharge, participants in the STS group will be contacted on a biweekly basis to inquire about their health status and assess their progress during their cardiac rehabilitation. They will be asked a series of questions related to smoking habits, adherence to medication and any symptoms they experienced. Data collected will be stored in a database that will flag abnormal responses and alert on-site cardiac nurses to respond as needed. This resulting interaction will be personalized, conversational and will vary in duration and context according to each individual patient’s needs and rehabilitation goals.

In both groups, patients will receive the standard level of care provided by the hospital to patients with heart failure. As part of their post-discharge care, patients will receive instructions and educational material detailing exercise and dietary recommendations. They will then be discharged to the care of their community physician or cardiologist. All patients will be given a 24-7 telephone number to access an advanced practice nurse with questions related to their care.

2.3 Allocation

Patients will be randomized in a 1:1 allocation ratio to TM+ versus TM alone. Randomization will be done in blocks randomly varying in size of 4 or 6 and will be stratified by centre. Stratification by centre was considered appropriate to account for the potential clustering of patients by centre, whereby the larger, more advanced sites may treat the more complex cases of heart failure. Stratifying according to centre also ensures that the observed effect of the intervention is due to the intervention itself and not the differing standards of care at each site.
Central randomization will be done using web-based technology. The centre coordinator will access this system and will provide pertinent information such as date of birth of the eligible patient to be randomized. The treatment allocation will then be assigned by this automated system.

2.4 Bias
This is a multi-centre prospective randomized open blinded endpoint trial (PROBE) design.\textsuperscript{32} The PROBE design has been used extensively in clinical trials in cardiology.\textsuperscript{33,34} It has been suggested that for PROBE design trials, hard endpoints should be used as the primary outcome.\textsuperscript{35} In this trial, the primary endpoint is a composite of all-cause mortality and hospitalization for HF.

The nature of this study does not allow us to use a double-blinded approach. However, it is important to note that part of the anticipated positive effect of telemedicine interventions actually requires that patients are aware they are more closely monitored due to it. Personnel conducting patients’ examinations at follow-up and collecting outcome data will be blinded to the intervention status and will not be involved in supporting the technical aspects of the intervention or in delivering the telemedicine services.

Additionally, we have taken the following steps to minimize biases:

- \textit{Selection bias} is addressed by allocation concealment using central randomization and strategies to ensure the assigned treatment is allocated to that specific patient.

- \textit{Performance and attrition bias} is minimized by ensuring that all patients receive the appropriate HF and cardiac treatment before entry into the study and that the patients continue to receive the standardized HF management in subsequent follow-up.
• *Detection bias* is minimized, as the primary endpoint of this study is a “hard endpoint” – all-cause mortality and hospitalization for HF; a blinded adjudication committee will adjudicate the causes of death and hospital admission. Standardized questions regarding hospitalization, adherence, smoking status as well as standardized anxiety and quality of life questionnaires will be used to minimize the bias and collection of these secondary outcome measures. These proposed measures will be in place to ensure that the detection of outcomes in the two groups is the same.

**2.5 Inclusion/exclusion criteria**

Eligibility will not differ according to whether or not patients participate in cardiac rehabilitation or other community exercise programs. Information regarding participants’ exposure to such programs will be obtained at baseline and verified at each follow-up visit. This will be done to account for the possible impact of interventions outside of telemedicine.

Patients meeting all of the following criteria are eligible for inclusion in the study:

1) Coronary artery disease patients with symptomatic heart failure (New York Heart Association [NYHA] Class II or III) characterized by impaired left ventricular function (Left Ventricular Ejection Fraction ≤ 45%) within the previous 12 months

2) Received optimal therapy for heart failure of at least 6 weeks (according to 2013 ACCF/AHA Guideline for the Management of Heart Failure)

3) Aged ≥ 18 years

4) Available via telephone for the duration of the study

5) Able to communicate in English or French
Patients will be excluded from the trial if they:

1) Coronary artery disease patients with preserved left ventricular function (left ventricular ejection fraction >45%)

2) Have New York Heart Association (NYHA) class IV heart failure symptoms

3) Had an acute coronary syndrome or coronary artery bypass surgery within 12 weeks

4) Have rheumatic heart disease, severe aortic or mitral valvular heart disease using the AHA/ACC guidelines

5) Have a medical condition likely to limit survival to < 1 year

6) Reside in a nursing facility

7) Are unable or unwilling to provide informed consent

2.6 Duration of follow-up

An accrual over 3 years with a minimal follow-up of 2 years was selected. This follow-up length will give a median follow-up of approximately 36 months. This is an adequate amount of time to observe if the intervention has lasting effect and will allow the intervention to provide benefit to this patient population.

Most of the studies that examined telemedicine for HF patients reported outcomes up to one year. There is a need for longer patient follow-up to better understand if the intervention has an instant effect or a more constant long-term one. If this intervention is to be implemented into clinical practice it is necessary to demonstrate that any observed positive effect is likely to last beyond the trial duration.
2.7 Frequency of follow-up

The patients will be followed at 2, 4 and 6 months and then every 6 months. A physical assessment and 6-minute walk distance will be performed at all follow-up visits. Assessments for smoking habits, adherence to medication, quality of life and anxiety will also be done at specified visits. These follow-up assessments periods are typical of cardiovascular trials and will allow for an interpretation of the interventions’ effect over time. Unlike previous trials however, the longer follow-up length of this study will determine whether or not the effect observed is a lasting one. See schedule of events (Appendix B) for details.

2.8 Outcome measures

2.8.1 Primary

All deaths and hospitalizations for HF will be recorded and reported to the coordinating centre with a detailed description of the circumstances surrounding the event on a case report form. An event adjudication committee co-chaired by a HF clinician-scientist and a clinician-scientist with extensive trial experience will determine the cause of death and the cause of hospital admission based on predetermined criteria. Data regarding mortality and readmission can be obtained at the provincial level by linking across the administrative databases of the hospitals within the province. Prior approval will be sought in order to obtain this data. See section 7 for details.

2.8.2 Secondary

Secondary outcomes of interest will include all-cause mortality, all-cause hospitalization, cardiovascular hospitalization, heart failure hospitalization, smoking cessation, medication
adherence, systolic blood pressure, low-density lipoprotein, exercise capacity and quality of life. See Section 2.9 for further details.

2.8.3 Safety Outcome Measures

Given the nature of this intervention, the only anticipated adverse effect is increased patient anxiety. This may occur as an unlikely result of the increased degree of monitoring compared to standard care. It may also result from the intervention requiring a more active involvement by the participants in their own care. Participants receiving structured telephone support are required to respond to a series of questions that include assessing their overall health, smoking habits, adherence to medication. Participants receiving telemonitoring are required to transmit daily measurements that include vital signs, electrocardiographic readings and weight measurements. Generalized anxiety disorder is an anxiety disorder that is defined as having “excessive, uncontrollable, unexplained and often irrational worry about everyday things that is disproportionate to the actual source of worry.” For diagnosis of this disorder, symptoms must last at least six months. As such, an external Data Safety Monitoring Board (DSMB) will assess the incidence of GAD at 6 and 12 months of follow-up.31

There are risks associated with the unsupervised exercising of heart failure patients. Any adverse events that include hospitalizations or deaths judged by the adjudication committee to have resulted from unsupervised exercise will be captured and analyzed using provincially linked administrative data on deaths and healthcare utilization.
2.9 Outcome measurement

Detailed operating manuals will be provided to each study centre by the coordinating centre. As part of the screening process, a patient’s most recent blood chemistry profile including liver, renal, and thyroid levels will be reviewed. If available, a point of care blood test to assess NT-proBNP levels will be performed with the patient’s informed consent at the screening visit. A proBNP kit will be used by the research team to obtain these blood samples. All samples will be disposed of immediately following the visit.

Data will be collected at baseline and at follow-up visits. After a qualified patient has consented for the study, a baseline clinical exam will be scheduled. The baseline visit will include: patient and cardiovascular history, a basic physical exam, 12-lead ECG, review of recent echocardiography (within the previous 12 months), anxiety and quality of life assessment, assessment of medication prescribed and taken by the patient, review of the patient’s most recent blood chemistry profile to assess liver, renal, thyroid functions (within the previous 6 months). To be able to measure and transmit vital signs measurements using a home monitoring device, all patients will be shown how to use the monitor at the baseline visit and will be asked to send daily measurements. Randomization will then occur following the completion of the baseline visit.

At each visit a medical history will be performed to ascertain if there have been changes of HF status, change in medications, and if there have been any hospitalization (defined as a health facility encounter that requires the patient to stay over 24 hours). A 12-lead ECG will be performed.
Four questionnaires will be completed: The Minnesota living with heart failure questionnaire (MLWHF) is an often used and validated disease specific quality of life (QOL) measure; EQ5D is a commonly used and validated generic QOL measure (Appendix C and D); Health Anxiety Inventory (HAI-18) is a validated generic anxiety measure (Appendix E); Generalized Anxiety Disorder 7-item (GAD-7) scale is a brief valid and reliable measure for assessing generalized anxiety disorder (Appendix F). In addition, the Specific Activity Scale Instrument will be collected (Appendix G). A 6 minute walk test will be performed and the walk distance will be collected (protocol to conduct the test is in Appendix H).

Weigh scales and blood pressure will all be electronic, and data will be transmitted by telephone lines to a central station that hold the electronic patient record at the Heart Institute. Similarly, information relating to smoking cessation, adherence to medication, and symptoms experienced will be collected for patients receiving the structured telephone support as part of the TM+ intervention. Smoking status will be biochemically verified 6 and 12 months of follow-up.

2.10 Health service research issues

A cost-utility analysis will be conducted with costs and quality adjusted life years (QALYs) based on the minimum follow-up period of this trial that is two years from entry. A second cost utility analysis will use a Markov model to assess long-term outcomes through an extrapolation of the data from the clinical trial. In both analyses, the cost effectiveness of telemonitoring plus regular telephone follow-up as compared with telemonitoring alone will be assessed according
to the incremental cost per quality adjusted life year (QALY) gained. All analyses will conform to Canadian guidelines for economic evaluation.\textsuperscript{44}

The analyses will both be conducted from the health care system perspective and resource use will be measured using questionnaires completed at the baseline visit and subsequent follow-up visits. A unit cost will be applied to each type of resource and the total cost will be estimated as the weighted sum of resource use. This is the sum of the product of the number of each resource item and its unit cost.

QALYs will be measured for each participant in the trial. This will be done by estimating utility values using the EQ5D instrument. The EQ5D instrument will be completed at baseline, six months and every six months afterwards until the end of the study. QALYs will then be assessed using area under the curve methodology and the utility values provided by participants. The primary analysis of cost per QALY will be obtained by calculating the difference in average costs of the two interventions divided by the difference in average QALYs. Resource items, their measurement as well as the source used for the information regarding cost are described in Appendix J.

2.11 Sample size

2.11.1 Event rate: Control Arm (rate control group)

In previous telemedicine trials, the control group received usual care and thus had a 30\% rate per year.\textsuperscript{36} For this study however, the control group is getting the current best form of telemedicine. The composite end point rate was therefore estimated to be 10\% per year.
2.11.2 Minimal Clinically Important Difference (MCID)

Previous telemedicine trials were reviewed for the selection of the relative risk reduction (RRR) for the MCID, in particular studies with a composite primary endpoint of mortality and heart failure hospitalization. The choice for RRR was 23% in the DIAL trial. However, given the more intensive nature of the new intervention, a larger RRR must be realized before this form of telemedicine should be adopted over the current best intervention. A RRR of 30% was selected based on a consensus of the Tele-HEART Trial investigators.

2.11.3 Power

The previous trials in telemedicine were reviewed for the selection of power. The DIAL trial is similar to this study in its design and its primary outcome. As with the DIAL trial, a power of 80% was selected.

2.11.4 Cross-over and Loss to Follow-up Rates

We consider cross-over from TM to TM+ to be a patient randomized to TM receiving structured telephone support alongside TM, and cross-over from TM+ to TM be a patient randomized to TM+ but only receiving the TM intervention with no structured telephone support. For this trial, we anticipate that no more than 2% cross-over will occur because the structured telephone support component is delivered by an automated calling system. As such, only the telephone numbers of patients randomized to the TM+ group will be entered into the system and will therefore receive this additional component. The loss to follow-up rate in previous telemedicine trials conducted at the Ottawa Heart Institute was approximately 5%. In these previous studies, the comparison group received usual care and had a slightly higher loss to follow-up rate. The loss to follow-up rate for this study was set at 2% for this trial because with
both groups receiving telemedicine interventions there will likely be even fewer patients dropping out from the comparison group.

2.11.5 Accrual and Follow-up

Based on a similar previously conducted large and multi-centred telemedicine trial with the same primary outcome, an accrual over 3 years with a minimal follow-up of 2 years was selected.\textsuperscript{36} A minimum follow-up of two years will give a median follow-up of approximately 36 months. This is an adequate amount of time to observe if the new intervention has lasting effect and to allow the intervention to derive any significant benefit for the patient population.

2.11.6 Sample Size Calculation

In order to detect a 30% relative risk reduction in the primary endpoint in the TM+ group, at alpha = 0.05 (two-sided) and 80% power, a sample size of 1000 patients will be needed (500 in the TM+ group and 500 in the TM only group). This calculation allows for a 2% cross-over rate as well as a 2% loss to follow-up in each group. This treatment comparison is based on the log-rank test. The sample size will be recalculated annually to make sure it accommodates any substantial changes in the overall event rate. The quasi-sequential procedure suggested by Betensky and the internal pilot study procedure suggested by Wittes will be considered and the sample size will only be increased (and not decreased).\textsuperscript{38,39}

2.12 Recruitment

A total of 1000 patients will participate in this study in a minimum of 14 centres. Patients will be randomized in a 1:1 ratio to each treatment arm. The estimated recruitment rate is 28 patients per month or a little over 2 patients per month per centre over 36 months.
There are currently fourteen centres part of the Ontario Telemedicine Network (OTN). The program roll out to 2200 patients in the North East, Central West and Toronto Central Local Health Integration Networks (LHIN) will expand to upwards of 30,000 patients in additional LHINs by 2015. Heart failure patients are among those eligible for program enrollment.

We also plan on compiling a list of other non-Canadian centres that may be included if enrolment is not up to expectation. Ahmed Kotb will be in charge of this task along with the steering committee members. Only centres with experience in clinical trials of telemedicine for heart failure patients will be invited to participate in this study.

2.13 Compliance

To a great extent, the benefit hypothesized to occur as a result of these telemedicine interventions depends on patients feeling encouraged, after receiving them, to become more actively involved in their own care through assessing their progress and sharing it with their clinicians. In both treatment arms, patients are expected to measure and transmit their vital sign measurements. Examining whether patients comply with these instructions will therefore be among the outcomes of interest and not an issue that will warrant special consideration or control.

2.14 Loss to follow-up

We anticipate loss to follow-up will not be more than 2%. In a recently completed telemedicine in heart failure trial the loss to follow-up was below 1%. Furthermore, the coordinating centre for this trial, the University of Ottawa Heart Institute, has had prior experience conducting similar trials in the past.
2.15 Centres involved

This is a multi-centre study with 14 participating centres across the Ottawa region (see Appendix I for further details regarding each centre). All fourteen of the included centres are part of the Ontario Telemedicine Network (OTN). OTN centres have experience offering a range of services that include the Telemedicine Local Health Integration Network (LHIN) Nurse program which brings together one hundred and ninety-one full time nurses across those fourteen member sites and the Telehome care program where nurses teach, coach and remotely monitor a patient’s health status using telemedicine. Heart failure patients are among those eligible for enrollment in their programs.

There will be an investigator and a study coordinator who will coordinate study activities at each included centre. Participating centres will be responsible for recruiting patients, completing and transmitting case report forms to the Coordinating Centre, completing patient follow-up visits, and collecting information on study outcomes.

2.16 Type of analyses

For the purposes of data analysis, three study populations will be considered: Intent-to-treat (ITT) Population, As-Treated Population and Per-Protocol Population. The ITT population will be used for the main analysis for all primary and secondary research questions, except for the safety analysis (secondary research question 4) where the as-treated population will be used. As secondary analyses, the analyses will be repeated for the as-treated and per-protocol populations.
2.16.1 Background and Demographic Characteristics

Background and demographic information will be summarized by means of frequency distributions (for categorical variables) and descriptive statistics of mean, standard deviation, minimum, median and maximum (for continuous variables). Background information will include age, sex, Left Ventricular (LV) ejection fraction, NYHA Class, use of Angiotensin Converting Enzyme (ACE) Inhibitors (ACEIs)/Angiotensin Receptor Blockers (ARBs), use of beta-blockers, diuretics, digitalis aldosterone antagonist, nitrates & vasodilators, diabetes, hypertension, history of coronary artery disease (angina, revascularization procedures, previous myocardial infarction), NT-proBNP level, and echocardiographic parameters: Left Atrium size and volume, and Left Ventricle mass, wall thickness and ejection fraction. Continuous variables will be tested for baseline comparability between the study groups using the t-test or Wilcoxon rank-sum test. Categorical variables will be tested for baseline comparability with the chi-square test or Fisher’s exact test.

2.16.2 Primary Analysis

The primary analysis (for the primary research question) will compare the time to the primary composite outcome of all-cause mortality or hospitalizations for heart failure in the TM+ arm versus TM alone arm. The primary outcome will be analyzed using survival analysis techniques. Kaplan-Meier product limit estimates will be used to summarize the survival experience (i.e. time-to-primary outcome) in each of the two groups and the nonparametric log-rank test procedure will be used for comparing the survival curves. The hazard ratio (HR) and associated 95 percent confidence interval (95% CI) will be calculated. The Cox’s proportional hazards model will be used to adjust for possible effects of covariates on survival.
2.16.3 Secondary Analysis

**For Secondary Objective 1:** TM+ vs. TM alone will be compared on the following 4 outcomes: time-to-all-cause mortality, time-to-all-cause hospitalization, time-to-HF hospitalization and time-to-CV hospitalization. These analyses will follow the survival analysis techniques outlined for the primary analysis. Both groups will also be compared on the hospitalization rate (i.e. number of hospitalization per unit time alive in the study). Adjusting for the possible effects of covariates, Poisson regression will be used to compare the rates between therapy groups for each of all-cause, HF and CV hospitalization.

**For Secondary Objective 2,** The TM+ arm will be compared to TM on smoking. Patients will complete a structured interview at baseline about the use of cigarettes, quit attempts, use of other nicotine containing products and other products/programs for smoking cessation. Smoking status will then be assessed at 6 and 12 months and abstinence will be defined as self-reported and biochemically verified for having not smoked (not even a puff) in the preceding 7 days, i.e. 7-day point prevalence abstinence. The NicAlert™ salivary cotinine test was used for biochemical validation of smoking status in patients reporting abstinence. Participants with saliva cotinine concentrations greater than 10 ng/ml were considered smokers. Participants who were lost to follow-up were coded as current tobacco users. It is important to note that the analysis of this outcome is expected to be underpowered due to the expected low prevalence of continued smoking among participants.

Adherence to medication is also commonly measured by self-reporting. In this trial, a Visual Analogue Scale (VAS) will be used, at 6 and 12 months follow-up visits, to measure adherence
by summing the total number of medication doses prescribed and taken, and dividing it by the total number of doses prescribed. Patients taking 90% or more of their prescribed medications as indicated will be considered adherent. The outcomes of smoking cessation and medication adherence will be compared between groups using chi-square and Fisher’s exact tests. The odds ratios (OR) and 95% confidence intervals will also be calculated. If there is any imbalance across the groups, these differences will be fitted as covariates in multiple logistic regression models and the adjusted odds ratios will be calculated.

Resting systolic blood pressure will be measured according to published guidelines using an Omron automatic sphygmomanometer. Fasting blood samples will be drawn according to the schedule of events (Appendix B). To obtain low-density lipoprotein (LDL) measurements, serum total cholesterol (TC) and triglycerides (TG) will be measured by enzymatic colorimetric methods high-density lipoprotein (HDL) will be measured directly using a homogeneous method and LDL will then be calculated by the Friedewald equation, except when TG exceeded 4.5 mmol/L. Lipid and blood pressure measurements will be tabulated and the mean, standard deviation, median and interquartile range (IQR) calculated. Therapy groups will be compared on these outcomes using the t-test or the Wilcoxon rank-sum test and 95% CI calculated. Repeated measures ANOVA will compare the two interventions on changes in systolic blood pressure and low-density lipoprotein levels over time (6 and 12 months).

For Secondary Objective 3, TM+ will be compared to TM on health related QOL (as assessed by MLWHF and EQ5D) and exercise capacity (as assessed by 6 minute walk distance). For each group, the frequency distribution for MLWHF, each of the domains of the EQ5D and the 6-
minute walk distance will be tabulated and the mean, standard deviation, median and interquartile range (IQR) calculated. Both groups will be compared on these outcomes using the t-test or the Wilcoxon rank-sum test and 95% CI calculated. Repeated measures ANOVA will compare the two interventions on changes in health related QOL and exercise capacity over time.

**For Secondary Objective 4**, a subgroup analysis will be conducted on: (a) male heart failure patients; (b) female heart failure patients; (c) heart failure patients aged 65 and older; and (d) heart failure patients younger than 65. For each of these subgroups, the TM+ group will be compared to the TM alone group on mortality and HF hospitalization using the survival analysis strategy outlined for the primary research question, as well as the Poisson regression comparing hospitalization rates outlined for secondary research question 1.

**2.16.4 Safety analysis**

**For Secondary Objective 5**, there is currently no data regarding the incidence of anxiety in heart failure patients as a result of receiving telemedicine. As such, measurements taken for anxiety, every 6 months, will be compared by baseline measurements for each group (TM+ vs. TM). Safety will be evaluated by documenting all cases of general anxiety disorder (measured by the GAD-7 scale) that occur in each arms as compared to baseline. Descriptive statistics (frequency distributions, numerical descriptors) and 95% CIs will be calculated. The outcome of GAD will be compared with baseline for each group using McNemar’s tests. Anxiety assessment (measured by the HAI-18) will also be collected (every 6 months) and compared to measures taken at baseline for each group. The difference from baseline will be compared using the
Wilcoxon signed-rank test for each arm. The as-treated population will be the main analysis population for this safety evaluation.

2.16.5 Economic Analysis

A cost-utility analysis will be conducted with costs and quality adjusted life years (QALYs) based on the minimum follow-up period of this trial that is two years from entry. A second cost utility analysis will use a Markov model to assess long-term outcomes through an extrapolation of the data from the clinical trial. In both analyses, the cost effectiveness of telemonitoring plus regular telephone follow-up as compared with telemonitoring alone will be assessed according to the incremental cost per quality adjusted life year (QALY) gained. All analyses will conform to Canadian guidelines for economic evaluation.44

The analyses will both be conducted from the health care system perspective and resource use will be measured using questionnaires completed at the baseline visit and subsequent follow-up visits. A unit cost will be applied to each type of resource and the total cost will be estimated as the weighted sum of resource use. This is the sum of the product of the number of each resource item and its unit cost.

QALYs will be measured for each participant in the trial. This will be done by estimating utility values using the EQ5D instrument. The EQ5D instrument will be completed at baseline, six months and every six months afterwards until the end of the study. QALYs will then be assessed using area under the curve methodology and the utility values provided by participants. The primary analysis of cost per QALY will be obtained by calculating the difference in average costs of the two interventions divided by the difference in average QALYs. Resource items, their
measurement as well as the source used for the information regarding cost are described in Appendix J.

2.17 Frequency of analyses
One interim analysis is planned when one-third of patients enrolled have been followed for a minimum of 1 year. A final analysis will be performed at the conclusion of the trial. An O’Brien Fleming alpha spending function was used to account for this interim analysis in the calculation of the required sample size.

2.18 Subgroup analyses
Subgroup analyses based on patient characteristics will be undertaken, primarily for sensitivity analyses to assess the robustness of the results, as well as for exploratory purposes for hypothesis generation. In particular, planned subgroups include: male vs. female; and age: 65 and above vs. under 65 years of age.

Patients in different age groups may benefit differently from telemedicine depending on how comfortable they may be with technology. Furthermore, it is of interest to determine if sex plays a role in patients’ willingness to be more actively involved in their own care. Analyzing according to sex will also examine if the questions asked as part of the telephone support intervention are differentially effective in both males and females.

2.19 Missing Data
Missing data will be considered to be missing at random (MAR) and will be handled using mixed methods repeated measures (MMRM) and multiple imputation (MI) techniques.
2.20 Previous pilot study

Given the successful completion of a number of randomized controlled trials involving telemedicine use at the University of Ottawa Heart Institute, no pilot study was conducted for this trial.\(^{37}\)

3. Trial Management

3.1 Management

Ahmed Kotb and The Cardiovascular Research Method Centre (CRMC) at the University of Ottawa Heart Institute (UOHI), under the direction of Dr. Wells, will coordinate the day-to-day management of the trial. Central randomization of patients and data collection will be implemented using CRMC’s web-based system. Data will be managed in and analyzed using SAS following the procedures developed for trials on telemedicine previously conducted at UOHI.\(^{37,43}\)

3.1.1 Data management responsibilities

Data management and randomization will be coordinated by the Cardiovascular Research Methods Centre (CRMC) of the University of Ottawa Heart Institute. More specifically, the CRMC will be involved in the following:

- Carrying out the web-based randomization and allocation;
- Developing online case record forms for data collection at baseline visit, follow-up visits, study exit visit, as well as protocol deviation forms;
- Designing and managing databases;
- Monitoring of data;
- Generating standard and study specific statistical reports;
The study will be conducted in accordance with the current approved protocol, ICH GCP, relevant regulations and standard operating procedures. Furthermore, the CRMC has standard operating procedures (SOPs) to help ensure good clinical practice and good laboratory practice related to the study methods, data management and integrity. Detailed operating manuals and data management manuals will be provided to each study centre.

3.1.2 Data capture methods
The CRMC will use its own readily available dedicated and secure web based electronic data capture system. This system will be tailored to the study specific workflow and will therefore make the management of questionnaire easy for both research staff and study participants. The planned stratified and block randomization will also be carried out using a flexible web-based randomization system that is part of the CRMC’s own data management system.

3.2 Steering committee
The applicant and co-applicants form the Steering Committee for this trial. The Principal applicant, Ahmed Kotb, will serve principal spokesperson for the study, chair the Committee and maintain communication within the study. Dr. Wells has extensive expertise and experience in the design and analysis of large multicenter clinical trials and will be head of the coordinating centre for this trial. Ms. Heather Sherrard is Vice-President of Clinical services at the coordinating centre and has led several clinical trials in telemedicine and cardiac rehabilitation.

Additionally, two clinician-scientists with extensive backgrounds in HF and in clinical trials will be identified to co-chair the clinical event adjudication committee. Another clinician-scientist
with extensive clinical trial experience will be required to serve as recruitment coordinator and oversee progress in recruitment, communicate with each participating centre and determine if increasing the number of centres will be necessary. Furthermore, two clinicians with extensive expertise in the management of HF will be in charge of advising and monitoring HF management in the trial. Finally, a clinician-scientist with clinical trial expertise will be helping Ahmed Kotb and Dr. Wells to monitor the performance of the coordinating centre, data collection, and to ensure that ongoing patient care is maintained.

3.3 Data safety and monitoring committee

A data monitoring committee (DMC) will be set up. The DMC will consist of three persons that will include: a HF specialist, a biostatistician with trial expertise and a scientist with extensive experience in cardiac rehabilitation. A charter governing the operations of the DMC will be developed in conjunction with DMC to determine specific procedures such as the frequency of reports/meetings and content of the safety analyses reports.

The charter will detail how the following issues will be handled:

- Adverse Events
- Serious Adverse Events
- Type and Duration of Follow-up of Subjects after Adverse Events
- Reporting Procedures
- Reporting of Pregnancy
3.3.1 Adverse Event (AE)

According to the Glossary of Clinical Research, an AE is any untoward medical occurrence in a patient or clinical investigation participants, which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign, symptom or disease temporally associated with the study, whether or not considered related to the study.

3.3.2 Serious Adverse Event (SAE)

According to the Glossary of Clinical Research, an SAE is any untoward medical occurrence that:

- Results in death,
- Is life-threatening,
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect.
- Other important medical events.

Given the nature of these interventions however, the only anticipated AE is increased patient anxiety. This may occur as an unlikely result of the increased degree of monitoring compared to standard care. It may also result from the intervention requiring a more active involvement by the participants in their own care. Participants receiving structured telephone support are required to respond to a series of questions that include assessing their overall health, smoking habits, adherence to medication. Participants receiving telemonitoring are required to transmit daily measurements that include vital signs, electrocardiographic readings and weight
measurements. Generalized anxiety disorder is an anxiety disorder that is defined as having “excessive, uncontrollable, unexplained and often irrational worry about everyday things that is disproportionate to the actual source of worry.” For diagnosis of this disorder, symptoms must last at least six months.\textsuperscript{31} As such, an external DMC will assess the incidence of GAD at 6 months from baseline and every 6 months after that. A detailed data monitoring/safety manual will be provided to each study centre by the coordinating centre and the collection of Serious Adverse Events will not commence until the patient is randomized.

3.4 Protocol deviations

Protocol violations and deviations will be reported promptly to the Research Ethics Board (REB) if they meet the following criteria:

\begin{itemize}
  \item[a)] If the protocol deviation is performed to eliminate an immediate hazard to the patient.
  \item[b)] If the change made to the protocol increases the risk to the patient and/or significantly increases the conduct of the trial.
  \item[c)] A copy of the deviations submitted to the REB will be filed.
\end{itemize}

3.5 Direct access to source data/documents

Direct access will be granted to authorized representatives from the sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections.

3.5.1 Source documents

Each participating centre must maintain appropriate medical and research records for this trial and ensure the protection of confidentiality of study patients.
The Principal Investigator is charged with making sure that the data collected are complete, accurate, and recorded in a timely manner.

Study data will be collected on study specific case report forms (CRF) and questionnaires will be completed during baseline and follow-up visits. Data will be entered into the web based system and stored electronically at the CRMC. Source documents and all forms will be stored at the individual study centres responsible for collecting the data. All Study information including paper files and computer software must be kept by the sponsor and at each participating study centre in a secure area, accessible only to study qualified personnel, for a maximum of 15 years.

All study material must have the ability to be recalled in the event of a future audit.

The study specific material to be stored includes but not limited to the following:

a) Centre study operations manual
b) All CRFs
c) All patients source documentation
d) All study related communications
e) Any other study related material.

3.6 Ethics review

The Investigators at each of the participating clinical centres will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki.

3.6.1 Institutional review board/ethics committee

A copy of this protocol, including amendments, informed consent forms, and questionnaires will be reviewed and approved by the Research Ethics Board (REB) or Institutional Review Board
(IRB) of each of the participating clinical centres. The IRB/REB will be notified of serious adverse event and protocol deviations related to patient safety by the investigator.

3.6.2 Informed consent

Before study inclusion, patients will be given detailed oral and written information about the principles and the protocol objectives of the study. The consent process will follow the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines as detailed in section 4.8. Patient information will be handled at all times in accordance with appropriate confidentiality standards and all applicable data protection and privacy laws.

3.6.3 Participant confidentiality

All patient related information will be kept strictly confidential. All records will be kept in a secure location that only research staff will be able to access. Patients will be identified only using a coded number that will be specific to each patient. All computerized databases will be password protected and will identify patients using these codes only.
References


and Metabolism; and the American Association of Cardiovascular and Pulmonary Rehabilitation. Circulation 2007;115(20):2675–82.


http://www.health.gov.on.ca/english/providers/program/ohip/sob/physserv/physserv_mn.html
Appendices

Appendix A. Study flow diagram

ASSESSED FOR ELIGIBILITY

Excluded:
- Preserved left ventricular function
- NYHA I or IV
- Had a major cardiac event in past 12 weeks
- Expected survival of < 1 year
- Reside in a nursing facility
- Unable or unwilling to provide informed consent

RANDOMIZATION & 1:1 ALLOCATION

TM

Patients included in the primary and secondary outcome analysis at follow-up

TM+

Patients included in the primary and secondary outcome analysis at follow-up
Appendix B. Schedule of Events

<table>
<thead>
<tr>
<th>Evaluation</th>
<th>Screening</th>
<th>Baseline/Randomization</th>
<th>Follow-up: 2 months</th>
<th>Follow-up: 4 months</th>
<th>Follow-up: 6 months and every 6 months</th>
<th>Exit Visit (end of study)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assessment of inclusion/exclusion</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Informed Consent</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Demographics</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NT-proBNP blood test</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Echocardiogram review (standard of care)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical History</td>
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<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Physical exam</td>
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<td>X</td>
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<td>6-minute walk test</td>
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<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Blood chemistry profile</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Medication assessment</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>12-lead ECG</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Quality of life questionnaires</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Adherence to medication</td>
<td>X</td>
<td></td>
<td></td>
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<td>X</td>
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<tr>
<td>Smoking status</td>
<td>X</td>
<td></td>
<td></td>
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<tr>
<td>Clinical events</td>
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<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Anxiety questionnaires</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>
Did your heart failure prevent you from living as you wanted during the past month (4 weeks) by -

<table>
<thead>
<tr>
<th>Item</th>
<th>No</th>
<th>Very Little</th>
<th>Very Much</th>
</tr>
</thead>
<tbody>
<tr>
<td>causing swelling in your ankles or legs?</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>making you sit or lie down to rest during the day?</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>making your walking about or climbing stairs difficult?</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>making your working around the house or yard difficult?</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>making your going places away from home difficult?</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>making your sleeping well at night difficult?</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>making your relating to or doing things with your friends or family difficult?</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>making your working to earn a living difficult?</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>making your recreational pastimes, sports or hobbies difficult?</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>making your sexual activities difficult?</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>making you eat less of the foods you like?</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>making you short of breath?</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>making you tired, fatigued, or low on energy?</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>making you stay in a hospital?</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>costing you money for medical care?</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>giving you side effects from treatments?</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>making you feel you are a burden to your family or friends?</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>making you feel a loss of self-control in your life?</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>making you worry?</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>making it difficult for you to concentrate or remember things?</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>making you feel depressed?</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>
Appendix D. EQ5D Questionnaire

Figure 1: EQ-5D-3L (UK English sample version)

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

**Mobility**
- I have no problems in walking about
- I have some problems in walking about
- I am confined to bed

**Self-Care**
- I have no problems with self-care
- I have some problems washing or dressing myself
- I am unable to wash or dress myself

**Usual Activities (e.g. work, study, housework, family or leisure activities)**
- I have no problems with performing my usual activities
- I have some problems with performing my usual activities
- I am unable to perform my usual activities

**Pain/Discomfort**
- I have no pain or discomfort
- I have moderate pain or discomfort
- I have extreme pain or discomfort

**Anxiety/Depression**
- I am not anxious or depressed
- I am moderately anxious or depressed
- I am extremely anxious or depressed
HAI

name: ______________________________                              date:

Each question is this section consists of a group of four statements. Please read each group of statements carefully and then select the one which best describes your feelings, over the past six months (or other agreed time period). Identify the statement by ringing the letter next to it, i.e. if you think that statement a.) is correct, ring statement a.). It may be that more than one statement applies, in which case, please ring any that are applicable.

1. a.) I do not worry about my health.
   b.) I occasionally worry about my health.
   c.) I spend much of my time worrying about my health.
   d.) I spend most of my time worrying about my health.

2. a.) I notice aches/pains less than most other people (of my age).
   b.) I notice aches/pains as much as most other people (of my age).
   c.) I notice aches/pains more than most other people (of my age).
   d.) I am aware of aches/pains in my body all the time.

3. a.) as a rule I am not aware of bodily sensations or changes.
   b.) sometimes I am aware of bodily sensations or changes.
   c.) I am often aware of bodily sensations or changes.
   d.) I am constantly aware of bodily sensations or changes.

4. a.) resisting thoughts of illness is never a problem.
   b.) most of the time I can resist thoughts of illness.
   c.) I try to resist thoughts of illness but am often unable to do so.
   d.) thoughts of illness are so strong that I no longer even try to resist them.

5. a.) as a rule I am not afraid that I have a serious illness.
   b.) I am sometimes afraid that I have a serious illness.
   c.) I am often afraid that I have a serious illness.
   d.) I am always afraid that I have a serious illness.

6. a.) I do not have images (mental pictures) of myself being ill.
   b.) I occasionally have images of myself being ill.
   c.) I frequently have images of myself being ill.
   d.) I constantly have images of myself being ill.
7. a.) I do not have any difficulty taking my mind off thoughts about my health.  
   b.) I sometimes have difficulty taking my mind off thoughts about my health.  
   c.) I often have difficulty in taking my mind off thoughts about my health.  
   d.) Nothing can take my mind off thoughts about my health.

8. a.) I am lastingly relieved if my doctor tells me there is nothing wrong.  
   b.) I am initially relieved but the worries sometimes return later.  
   c.) I am initially relieved but the worries always return later.  
   d.) I am not relieved if my doctor tells me there is nothing wrong.

9. a.) if I hear about an illness I never think I have it myself.  
   b.) if I hear about an illness I sometimes think I have it myself.  
   c.) if I hear about an illness I often think I have it myself.  
   d.) if I hear about an illness I always think I have it myself.

10. a.) if I have a bodily sensation or change I rarely wonder what it means.  
    b.) if I have a bodily sensation or change I often wonder what it means.  
    c.) if I have a bodily sensation or change I always wonder what it means.  
    d.) if I have a bodily sensation or change I must know what it means.

11. a.) I usually feel at very low risk for developing a serious illness.  
     b.) I usually feel at fairly low risk for developing a serious illness.  
     c.) I usually feel at moderate risk for developing a serious illness.  
     d.) I usually feel at high risk for developing a serious illness.

12. a.) I never think I have a serious illness.  
     b.) I sometimes think I have a serious illness.  
     c.) I often think I have a serious illness.  
     d.) I usually think that I am seriously ill.

13. a.) if I notice an unexplained bodily sensation I don't find it difficult to think about other things.  
     b.) if I notice an unexplained bodily sensation I sometimes find it difficult to think about other things.  
     c.) if I notice an unexplained bodily sensation I often find it difficult to think about other things.  
     d.) if I notice an unexplained bodily sensation I always find it difficult to think about other things.

14. a.) my family/friends would say I do not worry enough about my health.  
     b.) my family/friends would say I have a normal attitude to my health.  
     c.) my family/friends would say I worry too much about my health.  
     d.) my family/friends would say I am a hypochondriac.
For the following questions, please think about what it might be like if you had a serious illness of a type which particularly concerns you (e.g. heart disease, cancer, multiple sclerosis & so on). Obviously you cannot know for definite what it would be like; please give your best estimate of what you think might happen, basing your estimate on what you know about yourself and serious illness in general.

15. 
   a.) if I had a serious illness I would still be able to enjoy things in my life quite a lot.
   b.) if I had a serious illness I would still be able to enjoy things in my life a little.
   c.) if I had a serious illness I would be almost completely unable to enjoy things in my life.
   d.) if I had a serious illness I would be completely unable to enjoy life at all.

16. 
   a.) if I developed a serious illness there is a good chance that modern medicine would be able to cure me.
   b.) if I developed a serious illness there is a moderate chance that modern medicine would be able to cure me.
   c.) if I developed a serious illness there is a very small chance that modern medicine would be able to cure me.
   d.) if I developed a serious illness there is no chance that modern medicine would be able to cure me.

17. 
   a.) a serious illness would ruin some aspects of my life.
   b.) a serious illness would ruin many aspects of my life.
   c.) a serious illness would ruin almost every aspect of my life.
   d.) a serious illness would ruin every aspect of my life.

18. 
   a.) if I had a serious illness I would not feel that I had lost my dignity.
   b.) if I had a serious illness I would feel that I had lost a little of my dignity.
   c.) if I had a serious illness I would feel that I had lost quite a lot of my dignity.
   d.) if I had a serious illness I would feel that I had totally lost my dignity.

---

all groups are scored 0, 1, 2 or 3 depending on the statement selected; if more than statement is selected, use the highest-scoring statement of those chosen.

main section score (questions 1 to 14) =
negative consequences score (questions 15 to 18) =

**total score =**
scoring the 18 item HAI

In the 2002 paper describing the development of both the full Health Anxiety Inventory and this current shortened 18 item version, the following scores were reported for the shortened form in a series of different populations. The table below gives means (and standard deviations):

<table>
<thead>
<tr>
<th></th>
<th>health anxiety</th>
<th>anxiety sufferers</th>
<th>controls</th>
<th>students</th>
<th>gp patients</th>
<th>gastro patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>main section</strong></td>
<td>30.1 (5.5)</td>
<td>14.9 (6.2)</td>
<td>9.4 (5.1)</td>
<td>9.6 (4.5)</td>
<td>11.2 (4.6)</td>
<td>11.4 (6.3)</td>
</tr>
<tr>
<td><strong>negative consequences</strong></td>
<td>7.8 (2.8)</td>
<td>3.6 (2.2)</td>
<td>2.2 (2.1)</td>
<td>3.0 (1.8)</td>
<td>3.2 (2.0)</td>
<td>2.4 (1.9)</td>
</tr>
<tr>
<td><strong>total score</strong></td>
<td>37.9 (6.8)</td>
<td>18.5 (7.3)</td>
<td>12.2 (6.2)</td>
<td>12.6 (5.0)</td>
<td>14.5 (5.9)</td>
<td>13.9 (7.4)</td>
</tr>
</tbody>
</table>
Appendix F. GAD-7

<table>
<thead>
<tr>
<th>Over the last two weeks, how often have you been bothered by the following problems?</th>
<th>Not at all</th>
<th>Several days</th>
<th>More than half the days</th>
<th>Nearly every day</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Feeling nervous, anxious, or on edge</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>2. Not being able to sleep or control worrying</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>3. Worrying too much about different things</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>4. Trouble relaxing</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>5. Being so restless that it is hard to sit still</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>6. Becoming easily annoyed or irritable</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>7. Feeling afraid, as if something awful might happen</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

Column totals  +  +  +  = Total score

If you checked any problems, how difficult have they made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all Somewhat difficult Very difficult Extremely difficult

Scoring GAD-7 Anxiety Severity

This is calculated by assigning scores of 0, 1, 2, and 3 to the response categories, respectively, of “not at all,” “several days,” “more than half the days,” and “nearly every day.”

GAD-7 total score for the seven items ranges from 0 to 21.

0–4: minimal anxiety
5–9: mild anxiety
10–14: moderate anxiety
15–21: severe anxiety
Appendix G. Specific Activity Scale Instrument

Can you walk down a flight of stairs without stopping?
Yes □  No □

Can you carry anything up a flight of stairs without stopping or can you:
...shovel light snow?
...spade soil in garden or rake lawn?
...play sports like softball, basketball, soccer?
...ski downhill?
...walk at 4 mph on level ground?
Any Yes □  All No □
Check class 3 below

Can you shower without stopping or can you:
...strip and make beds?
...mop floors or sweep garage/walkway?
...walk 2.5 miles per hour?
...bowl or play golf?
...push power lawn mower?
...do light gardening?
All No □  Any Yes □
Check class 3 below

Can you carry at least 24 lbs up 8 steps without stopping or can you:
...carry heavy objects (at least 80 lbs)?
...play sports like cross country skiing, football, ice hockey or squash?
...jog or walk 5 mph?
...shovel heavy snow?
Any Yes □  All No □
Check class 1 below

Are you unable to get undressed without stopping?
No □  Yes □
Check class 4 below

Do you have symptoms when eating or when standing, sitting or lying relaxed?
No □  Yes □
Check class 4 below

Functional class (check one): □ Class 1, □ Class 2, □ Class 3, □ Class 4
Appendix H. Six minute hall walk test instructions

The 6-minute hall walk test (6 MHW) is a functional performance exercise that must be completed at baseline, and at follow-up visits.

The test will be conducted in an enclosed corridor that is:
- Free of traffic, obstacles and distractions
- A pre-measured 30.5 meters (100 feet) long length of corridor should be used for the test. Chairs should be placed at each end of the hallway.
- The hallway should be marked for ease of measurement. This will help to record the exact distance walked when the command to stop walking has been given.

Instruct the participant of the following:
- That the purpose of the test is to find out how far they can walk in six minutes
- That they should walk from end to end as many times as they can in six minutes
- That the most important part of the test is that you cover as much distance as possible in the 6 minutes
- That they can stop to rest if they need to, but they should remain in the same spot and resume when they are ready

During the test:
- The test administrator will need to record each pass from chair to chair during the 6 minutes

Post 6 MHW Test:
- The test administrator will need to count the lengths (distance one way) walked during the test time and the length of the partial lap completed

Data to be collected:
- Patient study number, date of the test, total distance walked on the case report form and whether or not the patient is symptomatic.
Appendix I. Participating Centres

The following thirteen satellite centres are affiliated with UOHI’s telehome monitoring program and will be participating in this trial:

<table>
<thead>
<tr>
<th>Centres</th>
<th>Capacity</th>
<th>Number of beds</th>
<th>Distance from UOHI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arnprior &amp; District Memorial Hospital</td>
<td>Community hospital, nursing home and medical centre with a staff of 300</td>
<td>105</td>
<td>62.8 km</td>
</tr>
<tr>
<td></td>
<td>Provides care for 30,000 residents</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carleton Place and District Memorial Hospital</td>
<td>Provides care for 25,000 residents</td>
<td>22</td>
<td>48.2 km</td>
</tr>
<tr>
<td></td>
<td>Ambulatory care clinics: 10, 750 visits annually</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Emergency room: 22, 000 visits annually</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cornwall Community Hospital</td>
<td>Emergency room: 55, 000 visits annually Total population served is 190,000</td>
<td>60</td>
<td>106 km</td>
</tr>
<tr>
<td>Deep River &amp; District Hospital</td>
<td>Emergency room: 10, 810 visits annually Total population served is 25,000</td>
<td>30</td>
<td>188 km</td>
</tr>
<tr>
<td>Hawkesbury &amp; District General Hospital</td>
<td>77 physicians 36, 549 emergency visits</td>
<td>96</td>
<td>99 km</td>
</tr>
<tr>
<td>Montfort Hospital</td>
<td>Emergency Department team treats over 50,000 patients of all ages every year</td>
<td>289</td>
<td>12.3 km</td>
</tr>
<tr>
<td>Pembroke Regional Hospital</td>
<td>Emergency Department visits 31,458 Active / Associate Physicians 50</td>
<td>180</td>
<td>142 km</td>
</tr>
<tr>
<td>Queensway Carleton Hospital</td>
<td>serves a population of over 400,000 1,800 health care professionals Emergency Visits – 72,516</td>
<td>264</td>
<td>10.9 km</td>
</tr>
<tr>
<td>Renfrew Victoria Hospital</td>
<td>Over 30,000 emergency and clinic visits per year 450 staff</td>
<td>54</td>
<td>91.9 km</td>
</tr>
<tr>
<td>St. Francis Memorial Hospital, Barry’s Bay</td>
<td>20-bed community hospital serving a population of 10,000</td>
<td>20</td>
<td>186 km</td>
</tr>
<tr>
<td>The Ottawa Hospital</td>
<td>1,300 Physicians 48,232 Patient Admissions 158,684 Emergency Visits</td>
<td>1155</td>
<td>9.2 km</td>
</tr>
<tr>
<td>Winchester District Memorial Hospital</td>
<td>Appointed Staff (includes physicians, dentists &amp; midwives): 135 Emergency visits: 23, 125 Ambulatory care visits: 16, 243</td>
<td>120</td>
<td>51.3 km</td>
</tr>
<tr>
<td>Perth &amp; Smiths Falls District Hospital</td>
<td>Serves 44,000 resident Emergency visits: 52,000 patients each year.</td>
<td>97</td>
<td>73.9 km</td>
</tr>
</tbody>
</table>
### Table 3. Description of resource items

<table>
<thead>
<tr>
<th>Resource item</th>
<th>Measurement</th>
<th>Information source for cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalization</td>
<td>Number of bed days by type of ward and principal diagnosis</td>
<td>Ontario Case Costing Initiative</td>
</tr>
<tr>
<td>In-hospital Medication</td>
<td>Drug, dosage and number</td>
<td>Hospital pharmacies</td>
</tr>
<tr>
<td>Out of hospital Medication</td>
<td>Drug, dosage and number</td>
<td>Provincial drug formulary&lt;sup&gt;45&lt;/sup&gt;</td>
</tr>
<tr>
<td>Physician consultation</td>
<td>Number by type of physician</td>
<td>Provincial fee schedule&lt;sup&gt;46&lt;/sup&gt;</td>
</tr>
<tr>
<td>Diagnostic tests</td>
<td>Number by type of test</td>
<td>Provincial fee schedule&lt;sup&gt;46&lt;/sup&gt;</td>
</tr>
<tr>
<td>Surgical procedures</td>
<td>Number by type of procedure</td>
<td>Ontario Case Costing Initiative</td>
</tr>
<tr>
<td>Medical device use (including telemonitoring equipment)</td>
<td>Number by type of device</td>
<td>Manufacturers and hospital finance departments</td>
</tr>
</tbody>
</table>

<sup>45</sup> Provincial drug formulary

<sup>46</sup> Provincial fee schedule
CHAPTER SIX: CLOSING REMARKS

The purpose of this thesis was to evaluate the impact of various forms of currently available telemedicine interventions with respect to clinical events, management of cardiac risk factors, and patient reported outcomes for individuals with heart diseases. This final chapter will bring together the results from our systematic review and meta-analysis (Chapter 3), network meta-analysis (Chapter 4) and discuss the design of a randomized controlled trial that will address an area in the evidence that requires further research (Chapter 5).

Discussion

Compared to the large number of reviews that have previously examined the impact of complex telemedicine interventions for individuals with advanced heart failure, there have been far fewer studies that specifically considered the effectiveness of the more basic regular telephone follow-up of individuals with less severe coronary artery disease conditions.

Typically, studies that examined this intervention were found to be small and underpowered to detect an effect. Systematically reviewing the evidence available and conducting a meta-analysis of these individual trials allowed for us to overcome this issue and provide a more specific evaluation of the benefit that telephone support can have for individuals who may not require close supervision and monitoring. Considered together with the results of two earlier reviews, our findings provide confirmation for the significant benefit of telephone support in encouraging smoking cessation, lowering systolic blood pressure and reducing symptoms of depression.\textsuperscript{1,2,3}
Despite the greater amount of evidence around the application of telemedicine in individuals with heart failure, the broad definition used for telemedicine has, in most cases, resulted in the inclusion of a variety of different interventions that were then compared with various standards of usual care. The conclusions drawn by different studies were therefore inconsistent. The only exceptions identified were of two earlier reviews that specifically focused on one well-defined form of telemedicine and compared it to usual care.\textsuperscript{4,5} In conducting a network meta-analysis, we were also able to avoid the inconsistency observed in previous studies that combined interventions that were inherently different. Their results are therefore consistent with those from our analysis that found no significant reduction associated with telemedicine in the likelihood of all-cause hospitalization when compared to usual care. Similarly, all three studies observed that telemonitoring can be effective in reducing the likelihoods of all-cause mortality and heart failure related hospitalizations.

Our multiple treatment comparison also found that structured telephone support interventions also reduced deaths and hospitalizations due to heart failure compared to usual care. Unlike the aforementioned reviews however, we were not limited, in the way that previous pairwise meta-analyses were, to only using available direct evidence that mostly compared telemedicine interventions with standard care. Our network meta-analysis therefore allowed for a more robust and precise comparison of several interventions as well as the inference of comparisons that had not yet been previously made. These results offer a better understanding of how the different forms of telemedicine currently available rank when compared against each other and not only standard care.
As part of this thesis, we also designed a randomized controlled trial that will compare the two applications of telemedicine that were found to be most effective, when delivered separately and in combination for coronary artery disease patients with or without heart failure. This study will add to the fairly limited number of individual studies identified by this thesis to have compared different forms of telemedicine against each other.  

**Recommendations**

Findings from this thesis highlight the need for a unified classification of these various forms of telemedicine to serve as guidance for conducting more specifically defined systematic reviews and meta-analysis on telemedicine in heart diseases. When multifaceted interventions are examined, it becomes difficult to determine specifically which method of telemedicine appears most effective for this particular patient population.

This meta-analysis has therefore allowed us to demonstrate the impact of a well-defined telemedicine intervention as it would compare to the current standard of care. For coronary artery disease patients whose condition is clinically judged to be well-managed, this basic form of telemedicine that is structured telephone support can have positive effects on reducing the likelihood of all-cause hospitalizations, aiding in smoking cessation, systolic blood pressure control and improving symptoms of depression and feelings of anxiety.

Findings from this thesis also highlighted the limited amount of evidence that compares these different types of telemedicine interventions with each other. It was for that reason that we were able to use standard care as a common comparator to infer indirect comparisons across these different forms of telemedicine. Conducting the network meta-analysis allowed for a
more comprehensive evaluation of the more complex forms of telemedicine that can be more appropriate for individuals with more advanced conditions such as heart failure. Two interventions, telemonitoring and structured telephone support, were considered to be superior for reducing the likelihood of death as well as hospitalization due to heart failure.

In order to verify these findings however, more studies of adequate power and follow-up lengths are needed that will directly compare these interventions against one another. The randomized controlled trial designed for this thesis will therefore provide a significant contribution to an area of the literature that continues to be understudied.
References


APPENDICES

Appendix A: The Cochrane Collaboration’s tool for assessing the risk of bias in randomized controlled trials.

<table>
<thead>
<tr>
<th>Domain</th>
<th>Description</th>
<th>Review authors’ judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sequence generation</td>
<td>Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.</td>
<td>Was the allocation sequence adequately generated?</td>
</tr>
<tr>
<td>Allocation concealment</td>
<td>Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during, enrollment.</td>
<td>Was allocation adequately concealed?</td>
</tr>
<tr>
<td>Blinding of participants, personnel and outcome assessments</td>
<td>Assessments should be made for each main outcome (or class of outcomes) Describe all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.</td>
<td>Was knowledge of the allocated intervention adequately prevented during the study?</td>
</tr>
<tr>
<td>Incomplete outcome data</td>
<td>Assessments should be made for each main outcome (or class of outcomes) Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomized participants), reasons for attrition/exclusions where reported, and any re-inclusions in analyses performed by the review authors.</td>
<td>Were incomplete outcome data adequately addressed?</td>
</tr>
<tr>
<td>Selective outcome reporting</td>
<td>State how the possibility of selective outcome reporting was examined by the review authors, and what was found.</td>
<td>Are reports of the study free of suggestion of selective outcome reporting?</td>
</tr>
<tr>
<td>Other sources of bias</td>
<td>State any important concerns about bias not addressed in the other domains in the tool. If particular questions/entries were pre-specified in the review’s protocol, responses should be provided for each question/entry.</td>
<td>Was the study apparently free of other problems that could put it at a high risk of bias?</td>
</tr>
</tbody>
</table>
Appendix B: SIGN – 50 Checklist for assessing the methodological quality of randomized controlled trials.

SIGN-50 for RCTs

<table>
<thead>
<tr>
<th>Section 1: Internal validity</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>In a well conducted RCT study...</strong></td>
<td><strong>In this study this criterion is:</strong></td>
</tr>
<tr>
<td>1.1 The study addresses an appropriate and clearly focused question.</td>
<td>□ Well covered □ Adequately addressed □ Poorly addressed □ Not reported □ Not addressed</td>
</tr>
<tr>
<td>1.2 The assignment of subjects to treatment groups is randomised</td>
<td>□ Well covered □ Adequately addressed □ Poorly addressed □ Not reported □ Not addressed</td>
</tr>
<tr>
<td>1.3 An adequate concealment method is used</td>
<td>□ Well covered □ Adequately addressed □ Poorly addressed □ Not reported □ Not addressed</td>
</tr>
<tr>
<td>1.4 Subjects and investigators are kept 'blind' about treatment allocation</td>
<td>□ Well covered □ Adequately addressed □ Poorly addressed □ Not reported □ Not addressed</td>
</tr>
<tr>
<td>1.5 The treatment and control groups are similar at the start of the trial</td>
<td>□ Well covered □ Adequately addressed □ Poorly addressed □ Not reported □ Not addressed</td>
</tr>
<tr>
<td>1.6 The only difference between groups is the treatment under investigation</td>
<td>□ Well covered □ Adequately addressed □ Poorly addressed □ Not reported □ Not addressed</td>
</tr>
<tr>
<td>1.7 All relevant outcomes are measured in a standard, valid and reliable way</td>
<td>□ Well covered □ Adequately addressed □ Poorly addressed □ Not reported □ Not addressed</td>
</tr>
<tr>
<td>1.8 What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?</td>
<td>□ Well covered □ Adequately addressed □ Poorly addressed □ Not reported □ Not addressed</td>
</tr>
<tr>
<td>1.9 All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention to treat analysis)</td>
<td>□ Well covered □ Adequately addressed □ Poorly addressed □ Not reported □ Not addressed</td>
</tr>
<tr>
<td>1.10 Where the study is carried out at more than one site, results are comparable for all sites</td>
<td>□ Well covered □ Adequately addressed □ Poorly addressed □ Not reported □ Not addressed</td>
</tr>
</tbody>
</table>

**SECTION 2: OVERALL ASSESSMENT OF THE STUDY**

2.1 How well was the study done to minimise bias? Code +++, +, -

**SECTION 3: OTHERS**

3.1 How was this study funded? List all sources of funding quoted in the article, whether Government, voluntary sector, or industry.

SIGN50 used by COMPUS
Appendix C: AMSTAR tool used to assess the methodological quality of systematic reviews

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
<th>Can't answer</th>
<th>Not applicable</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Was an 'a priorí' design provided?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>The research question and inclusion criteria should be established before the conduct of the review.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Was there duplicate study selection and data extraction?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Was a comprehensive literature search performed?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At least two electronic sources should be searched. The report must include years and databases used (e.g. Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reports (from the systematic review), based on their publication status, language etc.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Was a list of studies (included and excluded) provided?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A list of included and excluded studies should be provided.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. Were the characteristics of the included studies provided?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analyzed e.g. age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. Was the scientific quality of the included studies assessed and documented?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>'A priorí' methods of assessment should be provided (e.g. for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8. Was the scientific quality of the included studies used appropriately in formulating conclusions?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9. Were the methods used to combine the findings of studies appropriate?</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e. Chi-squared test for homogeneity, I²). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e. is it sensible to combine?).</td>
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<td>10. Was the likelihood of publication bias assessed?</td>
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<td>An assessment of publication bias should include a combination of graphical aids (e.g. funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test).</td>
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<td>11. Was the conflict of interest stated?</td>
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<td>Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.</td>
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Appendix D: RCT Evaluation Criteria and Headings

Evaluation Criteria

The RCT committee will take into account the following key questions when assessing each section of the application.

Section 1 - The need for a trial

Has the importance of the issue been adequately explained in terms of:

- Present and future resource implications for Canadian healthcare and the economy in general.
- Are the hypotheses to be tested and/or the study objectives specified and described clearly?
- Is the trial addressing the right question(s)?
- Is this the right time to conduct the trial with respect to current knowledge of the intervention and current use of existing technologies?
- Are the reasons for the study and the changes that might be implemented as a result of the study adequately explained?
- What evidence is available to inform the need for and design of this trial (e.g.: systematic reviews)?
- Is the proposed research compatible with the extent of the available knowledge, nationally and internationally?
- What impact will the results have on practice or our understanding of the proposed intervention or underlying condition?
- Will the results of the trial be generalizable beyond the immediate research setting of the trial in a way that will maximize the impact of the results?

Section 2 - The proposed trial

- Is the study design appropriate to answer the research questions posed?
- Has sufficient account been taken within the study design of the issues of generalizability and representativeness?
- What is the justification for the hypothesis underlying the power calculations?
- Are the outcomes, and their measures, clearly described and appropriate to the scientific hypothesis?
- Has the trial population been defined adequately in relation to the target population so that the results will have meaning?
- Have the measures been validated specifically for the target population(s)?
- Is the control group appropriate?
- How will sources of bias be avoided or taken account of?
Section 3 - Trial management

- Does the team of investigators proposed have the necessary range of disciplines and experience necessary to carry out the study?
- Does the trial team include people with experience in successfully running large multi centre trials?
- Has adequate statistical advice been sought and incorporated?
- Has adequate advice been sought and incorporated on other health services research issues if they are to be addressed?
- How will the trial be co-ordinated?
- What are the roles of members of the trial team?

Other Important Issues

Health Economics
CIHR does not require that health economic measures be included as outcomes in all its trials. However, it does require that a clear and informed justification of why these measures are to be either included or excluded.

Quality of Life
CIHR does not require that quality of life measures be included as outcomes in all its trials. However, it does require that a clear and informed justification of why these measures are to be either included or excluded.

Consumer Involvement in Trial Development
CIHR encourages the involvement of consumers and patient advocate groups with the aim of better trial design and greater acceptability of both trials and its findings.

Biological samples for future genetic analysis
The potential value of Randomized Controlled Trials as a source of well-characterized samples for future genetic analysis is being increasingly recognized and proposals for collection of this type of sample within a trial are welcomed. However, you should carefully consider the balance between the potential value of the samples and the impact on recruitment and logistics of the trial.

International Collaboration
Please discuss the nature of and need for international collaboration.

Patient Information Sheet
A draft patient information sheet and consent form should be appended.

Partners
If relevant, discuss the involvement of any proposed partner(s).
Headings

Applications submitted to the RCT committee **must** be structured according to the headings provided below.

Applications submitted to discipline-based committees are encouraged to use the headings but are not required to do so.

An entry is required under every heading. Failure to use the headings in an application submitted to the RCT committee will result in the administrative withdrawal of the application.

1. The Need for a Trial

1.1 What is the problem to be addressed?

1.2 What is/are the principal research question(s) to be addressed?

1.3 Why is a trial needed now? Evidence from the literature - see 1.4 below, professional and consumer consensus and pilot studies should be cited if available.

1.4 Give references to any relevant systematic review(s) and discuss the need for your trial in the light of the review(s). If you believe that no relevant previous trials have been done, give details of your search strategy for existing trials.

1.5 How will the results of this trial be used? E.g. Inform decision making/improve understanding.

1.6 Describe any risks to the safety of participants involved in the trial.

2. The Proposed Trial

2.1 What is the proposed trial design? E.g. Open-label, double or single blinded, etc.

2.2 What are the planned trial interventions? Both experimental and control.

2.3 What are the proposed practical arrangements for allocating participants to trial groups? E.g. Randomization method. If stratification or minimization are to be used, give reasons and factors to be included.

2.4 What are the proposed methods for protecting against sources of bias? E.g. Blinding or masking. If blinding is not possible please explain why and give details of alternative methods proposed, or implications for interpretation of the trial's results.

2.5 What are the planned inclusion/exclusion criteria?

2.6 What is the proposed duration of treatment period?

2.7 What is the proposed frequency and duration of follow up?

2.8 What are the proposed primary and secondary outcome measures?
2.9 How will the outcome measures be measured at follow up?

2.10 Will health service research issues be addressed? Justify inclusion/exclusion of health economics and quality of life measures. If these measures are to be included full details should be given including power calculations.

2.11 What is the proposed sample size and what is the justification for the assumptions underlying the power calculations? Include both control and treatment groups, a brief description of the power calculations detailing the outcome measures on which these have been based, and give event rates, means and medians etc. as appropriate.

N.B. It is important to give the justification for the size of the difference that the trial is powered to detect. Does the sample size calculation take into account the anticipated rates of non-compliance and loss to follow-up given below?

2.12 What is the planned recruitment rate? How will the recruitment be organized? Over what time period will recruitment take place? What evidence is there that the planned recruitment rate is achievable?

2.13 Are there likely to be any problems with compliance? On what evidence are the compliance figures based?

2.14 What is the likely rate of loss to follow up? On what evidence is the loss to follow-up rate based?

2.15 How many centers will be involved?

2.16 What is the proposed type of analyses?

2.17 What is the proposed frequency of analyses?

2.18 Are there any planned subgroup analyses?

2.19 Has any pilot study been carried out using this design?

3. Trial Management

3.1 What are the arrangements for day to day management of the trial? E.g. Randomization, data handling, and who will be responsible for coordination.

3.2 What will be the role of each principal applicant and co-applicant proposed?

3.3 Describe the trial steering committee and if relevant the data safety and monitoring committee.