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Innovative telemonitoring enhanced care program for chronic heart failure (ITEC-CHF) to improve guideline compliance and collaborative care: protocol of a multicenter randomized controlled trial

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ABSTRACT

Introduction: Chronic heart failure (CHF) is a life-threatening chronic disease characterised by periodic exacerbations and recurrent hospitalisations. In the management of CHF, patient compliance with evidence based clinical guidelines is essential, but remains difficult practically. The objective of this study is to examine whether an innovative telemonitoring enhanced care program for CHF (ITEC-CHF) improves patients' compliance, and associated health and economic outcomes.

Methods and Analysis: A multicentre randomized controlled trial (RCT) has been designed. Patients will be recruited and randomized to receive either ITEC-CHF (n=150) or usual care (UC-CHF) (n=150) for at least 6 months. ITEC-CHF combines usual care and an additional telemonitoring service including remote weight monitoring, structured telephone support, and nurse-led collaborative care. The primary outcomes are the compliance rates with best-practice guidelines for daily weight monitoring. The secondary outcomes include the compliance with other guideline recommendations (health maintenance, medication, diet, and exercise), health (health related quality of life, risk factors, functional capacity, and psychological states), and economic outcomes (risks of hospital readmission, general practitioner/emergency department visits, and cost benefits).

Ethics and Dissemination: The clinical trial has been approved by Peninsula Health Human Research Ethics Committee (HREC Reference: HREC/14/PH/27), Royal Perth Hospital Human Research Ethics Committee (Reference: 15-081), and the Curtin University Human Research Ethics Committee (Reference: HR 181/2014). We will disseminate the final results to the public via conferences and journal publications. A final study report will also be provided to the ethics committees.

Trial registration: Registered with Australian New Zealand Clinical Trial Registry (Trial ID: ACTRN 12614000916640).

Key words: chronic heart failure, telemonitoring, internet, compliance

Strength and limitations of this study

1. The first multicentre randomized controlled trial to evaluate the effects of telemonitoring on patient compliance with guideline-advocated self-management, and associated clinical outcomes.
2. Special focus on addressing the well-known issue of patient noncompliance with daily weight management.
3. Novel "zero-touch" design to prevent any technical difficulties and weight monitoring burdens to participants.
4. Integration with best-practice clinical workflows and action plan to streamline the intervention processes and minimize the workload to the care providers.
5. The study is limited to a 6-month intervention, potentially insufficient for analysis of long-term effects on patient compliance and health outcomes.

INTRODUCTION

Congestive heart failure (CHF), a life-threatening chronic disease, is a global pandemic[1]. It affects over 26 million people[2] with annual direct costs of over $65 billion globally[3]. Despite advances of modern medicine, patients with CHF continue to experience poor survival (30% to 50% at 5-years[4,5]), debilitating symptoms such as dyspnoea and fatigue[6], poor health related quality of life (HQoL)[7], and episodic clinical exacerbations with high risks of hospitalization[8,9].

To effectively manage CHF, evidence-based guidelines are available internationally[10,11]. A consistent recommendation of guidelines is self-management, such as fluid restrictions and daily weighing to monitor fluid balance[12]. Patient compliance with such clinical guidelines is essential to optimise health outcomes[13], but is often suboptimal[14,15]. For example, 12%-75% of patients in usual care were found to adhere to the cardinal recommendation of daily weighing [15,16]. Noncompliance is likely due to a variety of factors including time constraints[17], insufficient knowledge[18], and limited clinical support[19]. Importantly, patients who are noncompliant with self-management guidelines often fail to effectively engage with clinicians for timely interventions [16] resulting in an increased risks of mortality[20], and hospital readmissions[21,22].

Telemonitoring applications are an evolving strategy to improve CHF care, which have the potential to support patients in self-management[23,24,25]. However the effect of telemonitoring on patient compliance with guideline-advocated self-management has not been extensively studied. To our knowledge, only four RCTs have compared patient compliance between a telemonitoring intervention and usual care group[26,27,28,29]. These trials were limited by small sample sizes (n≤100) or short duration follow-up (≤3 months). Furthermore, their outcomes are inconsistent, with two trials reporting improved patient compliance [26,27] and two reporting no benefit[28,29]. Because of the limited and inconsistent evidence, no meta-analysis studies or reviews have been able to conclude the effectiveness of using telemonitoring to improve patient compliance. These facts highlight the need for further research to substantiate patient compliance in telemonitoring studies for CHF care.

To address the issue of patient noncompliance, we have designed an Innovative Telemonitoring Enhanced Care program for CHF (ITEC-CHF). This program focuses on assisting patients with CHF in complying with the daily weight management recommended by the guidelines. To minimise weight monitoring burdens and technical difficulties, the program proposes a novel "zero-touch" design, meaning that the participants are not required to interact with the technology other than stepping onto a scale for weight measurement as in usual care, and they don't need to learn extra knowledge and skills to receive the telemonitoring intervention. The program is also integrated with existing best-practice clinical workflows and action plan to streamline the intervention and make it seamless for care providers.

To evaluate the program, we will conduct a multicentre RCT. The objective of the trial is to examine the hypothesis that the ITEC-CHF program improves patients' compliance, and associated health and economic outcomes. This trial will be the first to examine the patient compliance of an innovative telemonitoring program across different care settings. It will also add essential clinical evidence to support use of telemonitoring applications in the community.

METHOD

Trial design

A prospective two-arm multicentre RCT has been designed. In the trial, patients with CHF will be recruited at two trial sites: 1) Frankston Hospital and Rosebud Hospital in Victoria (VIC), Australia, and 2) Royal Perth Hospital and Fiona Stanley Hospital in Western Australia (WA). The ethics application for the trial site in VIC has been approved by Peninsula Health Human Research Ethics Committee (HREC Reference: HREC/14/PH/27), and the ethics applications for Royal Perth Hospital and Fiona Stanley Hospital have been approved by Royal Perth Hospital Human Research Ethics Committee (Reference: 15-081) and the Curtin University Human Research Ethics Committee (Reference: HR 181/2014). The multicentre RCT trial has been registered in the Australian New Zealand Clinical Trials Registry (Trial ID: ACTRN12614000916640).

The participants in the trial will be individually randomized to receive either ITEC-CHF or usual care (UC-CHF) for at least 6 months. The allocation ratio of the randomization is 1:1. The randomization is stratified by the two trial sites (VIC and WA) to ensure the allocation ratio in each site. According to a recommended method[30], a series of random allocation assignments with permuted blocks have been generated, and sealed in opaque envelopes. The block sizes will be kept confidential to prevent potential prediction of the assignments. Data analysts generated the randomization sequence, and will be blinded throughout the trial using de-identified patient data.

The trial flow diagram is presented in Figure 1. Through the trial, project nurses at the trial sites will use their electronic patient administration systems to screen patients with CHF, and send an invitation letter to eligible candidates. One week later, project nurses will follow up with the candidates via a telephone call. If a candidate is willing to participate in the trial, the project nurses will arrange a face-to-face interview. During the interview, project nurses will explain the trial processes and requirements in detail, and conduct formal written consent with the candidates who agree to participate in the trial. Participants recruited will be interviewed by the project nurses for a baseline assessment. Each participant will then be randomized into either ITEC-CHF or UC-CHF group. At the 6-month time point, all participants will be assessed again. After the 6-month assessment, if the participants are willing to continue, they can stay in the trial to receive a 12-month assessment. Finally, the project nurses will collect the trial data for the research analysis. Participants will be enrolled from January 2015 to October 2017.

Figure 1.

Inclusion and exclusion criteria

Patients will be eligible to participate in the trial, if they satisfy all the following inclusion criteria: 1) CHF diagnosed by a clinician with an ejection fraction (EF) ≤40%, 2) able to weigh themselves safely, 3) at least 18 years of age, 4) have a regular personal general practitioner (GP) or agree to use a designated GP, 5) with a permanent residential address, and 6) without significant cognitive impairments. Patients will be excluded if

they meet any of the following criteria: a) expected survival < 12 months, b) end stage renal failure on dialysis, c) long term nursing home resident, or d) participating in any other clinical trial.

Trial interventions

Usual care

Participants in the UC-CHF group will receive a standard package of paper-based diary and booklets at baseline, including the "Living Well with Chronic Heart Failure" resource produced by the Heart Foundation of Australia (HFA). They will then attend standard CHF clinics and primary care physicians and undertake traditional CHF self-management through the trial period. Each participant will also be provided with an electronic weighing scale (ForaCare, W550, CA, USA), and asked to use the weight scale according to the self-management recommendation of the HFA. Project nurses will visit the participants to download the weight data from the weight scale at scheduled times, approximately every three months.

Enhanced care

The ITEC-CHF program will combine usual care and an additional telemonitoring service. The telemontioring service consists of three major components: remote weight monitoring, structured telephone support, and nurse-led collaborative care. The service is integrated with a telephone call centre (MePACS, VIC, Australia) [31], and a nurse care service according to their workflows in usual care.

The integrated care model of the ITEC-CHF program is shown in Figure 1. In the model, participants are provided with an electronic weighing scale (ForaCare, W550, CA, USA), and a computer tablet (Samsung, Galaxy Tab A, Korea). They are asked to use the scale to measure their body weight daily, immediately after wake-up, following voiding, without shoes, in light clothing, and before the next dose of medication. The measured weight entry is recorded in the scale, and then automatically transmitted to the tablet via a wireless Bluetooth function embedded in the scale. The tablet is preloaded with an Android application (Medtech Global, VIC, Australia). This application receives the weight entry, and uploads the entry to a proprietary software package, called Manage My Health (MMH) (Medtech Global, VIC, Australia). A web application in MMH automatically monitors uploaded weight entries in real time to generate alerts, and triage the alerts to project nurses and the telephone call centre. The rules to generate and triage the alerts are given in Table 1. They were designed in accordance with the HFA guidelines for the prevention, detection and management of CHF in Australia[10].

Operators at the call centre will respond to the alerts in real time (24 hour, 7 days a week). If a participant does not weigh before 10AM, a call operator will call the participant to remind him/her to weigh. During the call, if the participant needs clinical support such as advice for assessing CHF symptoms or managing diet, the call operator will arrange a nurse follow-up. The project nurses will subsequently follow up with the participant via a telephone call or home visit if needed. The call operators also provide technical support through the trial, such as updating the tablet application, and arranging home visits to change batteries in the scales.

The project nurses provide structured interventions according to three types of alerts: rapid weight fluctuation (±2 kg in 2 days), slow weight fluctuation (±5 kg in 28 days), and low-risk weight fluctuation (±1 kg over 24 hours). If a participant has rapid weight fluctuation, a project nurse will be alerted. The nurse will then call the participant to assist him/her in assessing critical symptoms, and activating the CHF action plan if indicated, such as attending their GP, CHF clinic or presenting to an emergency department (ED). For an alert of slow weight fluctuation, the project nurses will assist the participant in assessing CHF symptoms, and arranging clinical review at the participants' GP or CHF clinics. The option to present to an ED may also be applied, if this is clinically indicated. If a participant's body weight fluctuation exceeds ±1 kg (but is less than ±2 kg) over 24 hours, a questionnaire will be automatically triggered and sent to the participant's computer tablet. The user interface of the questionnaire is shown in Appendix 1. If the participant reports any of the clinical conditions in the questionnaire or does not respond to the questionnaire, the project nurses will follow up with the participant for a clinical assessment.

Figure 2.

Table 1.

Primary and secondary outcomes

The outcome measures of the trial are given in Table 2. The primary outcome will be compliance with daily weight monitoring as evaluated by weight entries, recorded on the electronic scales provided to both the ITEC-CHF and UC-CHF groups. Based on a published study[14], we define that a participant is compliant with daily weight monitoring, if he/she performed weight monitoring at least 4 days a week. The rate of the time for each participant to comply with daily weight monitoring during his/her trial period will also be computed; and the histogram of the rate will be analysed. The secondary outcomes will include compliance with other guideline recommendations (health maintenance, medication, diet, and exercise), health (health related quality of life, risk factors, functional capacity, and psychological states), and economic outcomes (risks of hospital readmission, general practitioner/emergency department visits, and cost benefits). We will also use a validated questionnaire[32] to evaluate the guideline recommendations. Patients' characteristics and assessment records will be collected by the project nurses. For evaluation of hospital readmissions and ED presentations, the data will be extracted from electronic patient administration systems of the hospitals in the trial.

Table 2.

Sample size

Compliance with daily weight monitoring was used to calculate the sample size. The null hypothesis is that the percentage of "compliant" participants in the ITEC-CHF group is not higher than in the UC-CHF group. To reject the null hypothesis, we assumed a compliance rate of 80% in ITEC-CHF, and 65% in UC-CHF. We also assumed an attrition rate of 10%. A two-tailed test with a power of 90% and Alpha of 0.05 was used to calculate the same size to achieve a statistical significance[33]. The power calculation resulted in that the study needs at least 143 participants in each group. Accordingly, we rounded the calculated sample size, and made the

trial size of 150 patients in each group, for a total of 300 participants. With this sample size, we have a likelihood of 90% to yield a statistical significance.

Statistical analysis

A Chi-square test will be used to compare categorical variables between the ITEC-CHF and UC-CHF group, such as sex, and compliance (compliant patients vs noncompliant patients). ANOVA will be applied to analyse continuous variables such as age and weight variations. A Cox proportional hazards model will be performed to analyse the risks of hospital readmission and ED visits. The analysis will be adjusted for confounding variables including sex, age and trial sites. The confidence interval of 95% will be estimated. A p-value less than 0.05 will be considered as statistical significance for all tests. The statistical analysis will be conducted using SPSSv23. Missing data at the case level will be imputed using a multiple imputation method in the SPSS.

Discussion

Daily weight monitoring is a Class I recommendation in the management of CHF[11] to help maintain fluid balance. Fluid retention is an early sign of acute CHF deterioration, a flag for poor compliance with prescribed medication (especially diuretics) and non-adherence with fluid and salt restrictions. Early identification of abnormal weight fluctuations caused by fluid accumulation allows clinicians to work with the patient to improve their compliance, and provide timely interventions. This potentially reduces the burden of heart failure in terms of reducing preventable hospitalizations and preventing clinical deteriorations amongst patients with CHF [22,34,35].

In usual care, patients often have difficulties using paper based diaries to record daily weight entries, and analyse recorded weight entries in association with observed symptoms in order to seek clinical interventions. Weight monitoring in isolation also requires patients to have the knowledge and skills to effectively identify symptoms, make decisions about their clinical relevance, and act on these. To overcome these difficulties, this study proposes the ITEC-CHF program to automatically detect abnormal weight fluctuations, and provide active clinical support through a call centre and project nurses. Compared with the traditional management of CHF, this program has the potential to dramatically simplify the daily weight monitoring and management, and does not require special knowledge or skills. While engaging with the patients for interventions of abnormal weight fluctuations, the project nurses have opportunities to assess patients' health, and issues of compliance with other recommendations, such as diet, fluid restriction, medication, exercise, and collaborative care. We anticipate that this will allow the nurses to actively engage with patients, and provide a broad range of clinical interventions for the management of CHF. Through the improved compliance and clinical support, it is expected that patients will actively engage with well-established multidisciplinary clinical services for further treatment or care such as titration of diuretic medication.

The efficacy of the program will be evaluated through a multicentre RCT. The evaluation is focused on the improvement in patient compliance and associated outcomes. To accurately evaluate the compliance with daily weight monitoring, objective weight data will be obtained from both intervention and control groups. A validated questionnaire will also be used to assess participant compliance with other important self-management

behaviours, as recommended by CHF guidelines[10]. In addition to compliance, the questionnaire will also assess barriers to self-management of CHF more broadly. This will help in the refinement of telemonitoring to support CHF care in future clinical practice.

If the efficacy is validated, use of the ITEC-CHF program will not only improve the patient compliance and health outcomes, but also provide an easy way for care providers to effectively and efficiently engage with patients for collaborative care, especially for patients in rural and remote areas. Based on the ITEC-CHF program, other telemonitoring devices such as ambulatory electrocardiogram, glucose meters and blood pressure monitors can also be easily integrated to provide broader interventions for CHF patients with cardiac conditions and comorbidities including diabetes and hypertension. Therefore, validation of the system for weight compliance would support further exploration of telemonitoring for improving CHF care, as well as other chronic conditions.

The study is limited to the 6-month intervention. The 6-month duration is potentially insufficient to reflect real long-term effects of the program through the ongoing management of CHF. Recent studies, in fact, have already demonstrated an issue of declined patient adherence overtime[36,37]. Therefore, extra caution will be exercised when interpreting the outcomes of this study.

Summary

This study proposes an innovative telemonitoring program focusing on improving compliance with evidence based clinical guidelines for the self-management of CHF. To our knowledge, this study will be the first to use a multicentre RCT to evaluate the effects of a telemonitoring program on compliance, and associated clinical benefits. The evaluation will provide a unique opportunity to investigate the benefits and barriers of using telemonitoring to improve the management of CHF, and will provide important findings to further improve telemonitoring applications for CHF care in the community.

Author contributions

This study protocol was mainly developed by H.D, A.D, I.E, and R.J. The first draft of the manuscript was written by H.D and R.J. All other authors contributed to design of the clinical study, and/or critical revision of the manuscript.

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Conflicts of interest

We declare that there are no conflicts of interest in the clinical trial.

Acknowledgement

The authors gratefully acknowledge 1) members of the Project Control Board, including Mr. David Anderson, Dr Phil Carrillo, Dr. Jamie Layland, Dr. Fergus McGee, Mr. Mark Gravell, Ms Alison Dowling for their management and guidance in the clinical trial, 2) members of MePACS, including Mr. Dean Richardson, Mr. Dhruv Singh for implementing the telemonitoring system, and managing the call service in the clinical trial, 3) members of Medtech Global, including Mr. Rama Kumble and G.K Shridhar for implementing and managing the telemonitoring system in the clinical trial, and 4) nursing and medical support provided by Julie Smith and Dr Matthew Best from the trial site in WA.

Appendix 1.

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Captions:

Figure 1. Trial flow diagram of the two-arm randomized controlled trail to compare the ITEC-CHF program with usual care.

Figure 2. The care model of the ITEC-CHF program is integrated in usual care. The integration includes: 1) remote weight monitoring, 2) structured telephone support, and 3) nurse-led collaborative care.

Table 1. Alerts generated, and associated interventions provided in the ITEC-CHF program.

Table 2. Trial outcome measures and assessment tools and data resources.

Appendix 1: User interface of the questions sent in the event of a low-level alert.

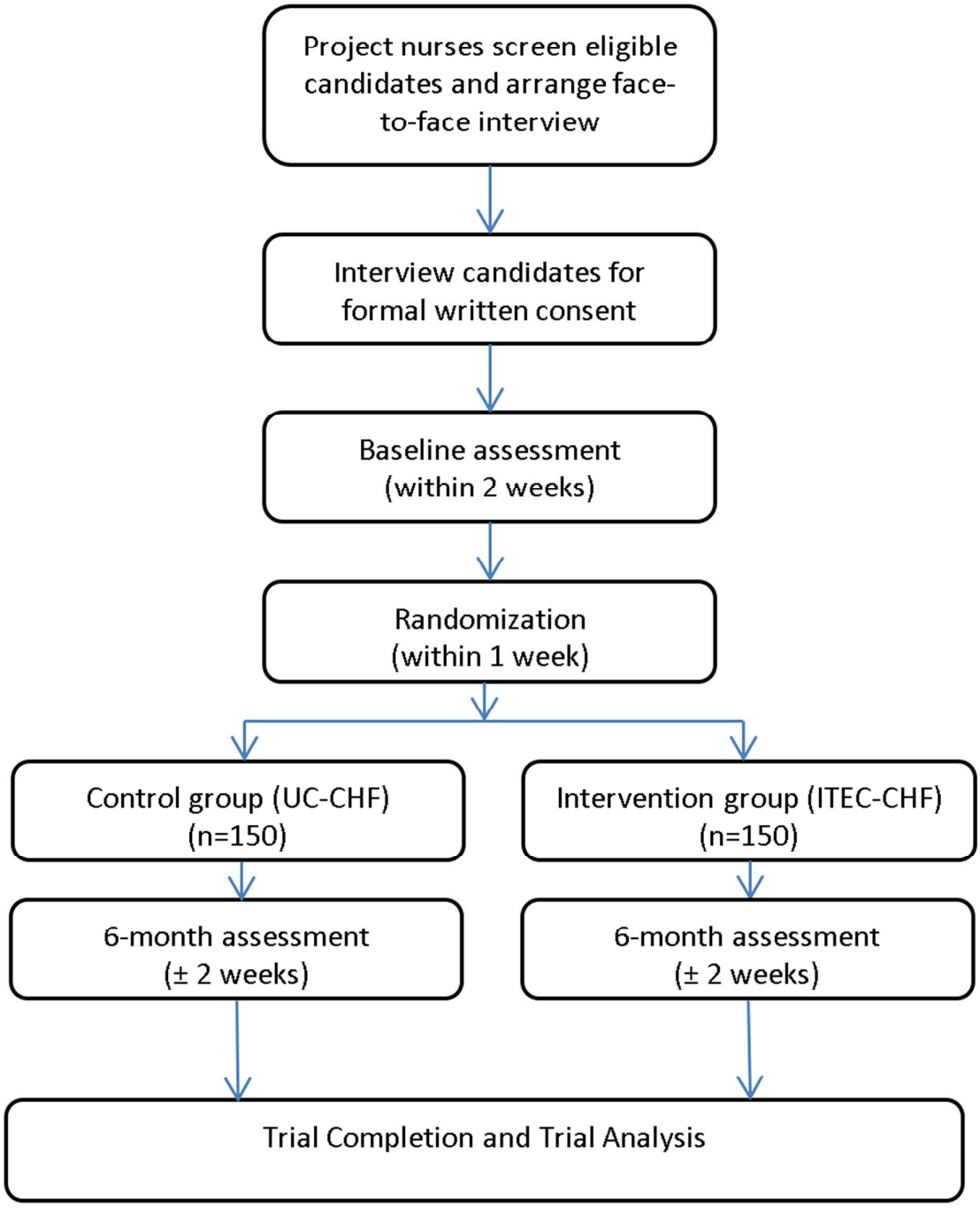


Figure 1.

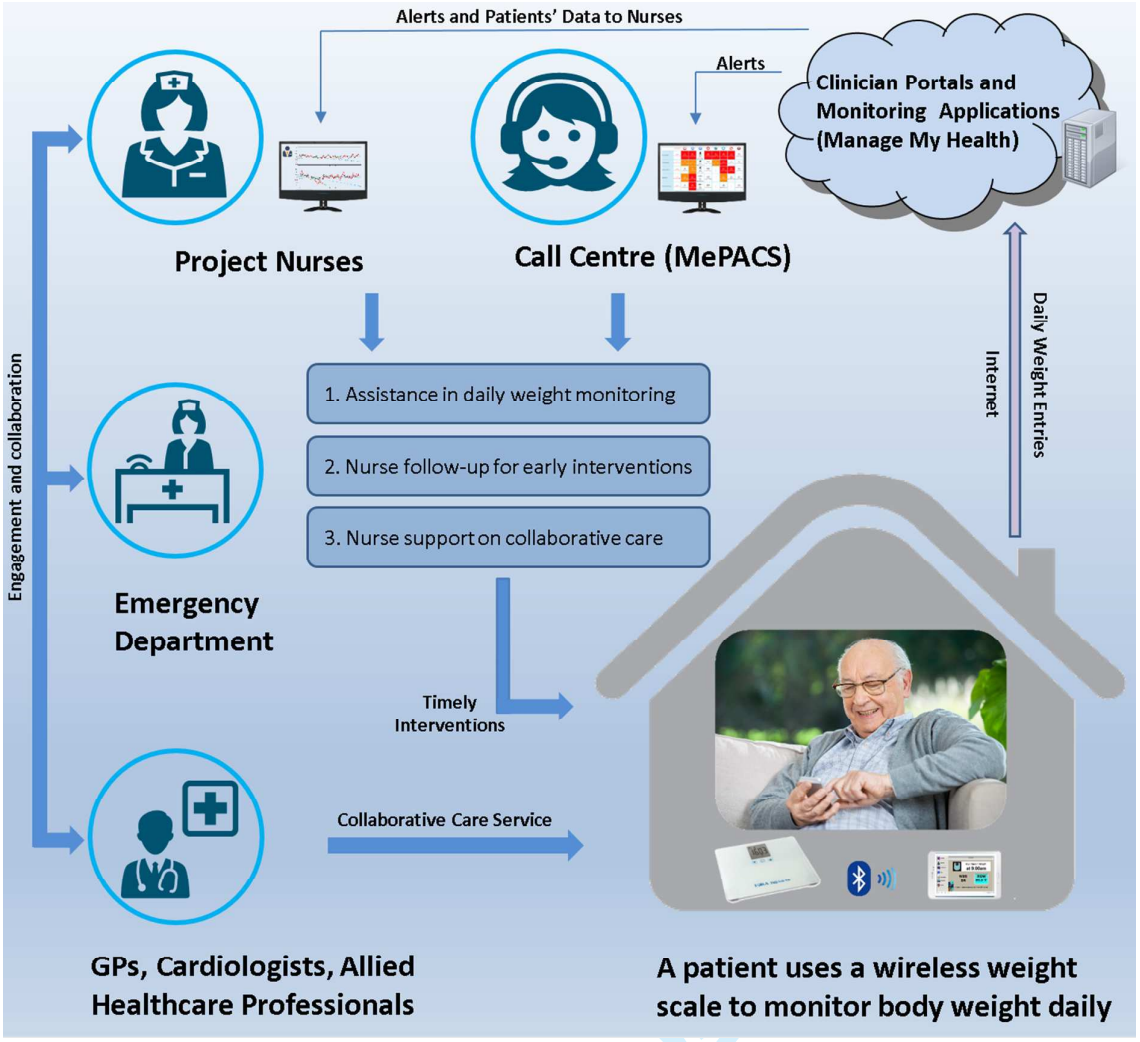


Figure 2.

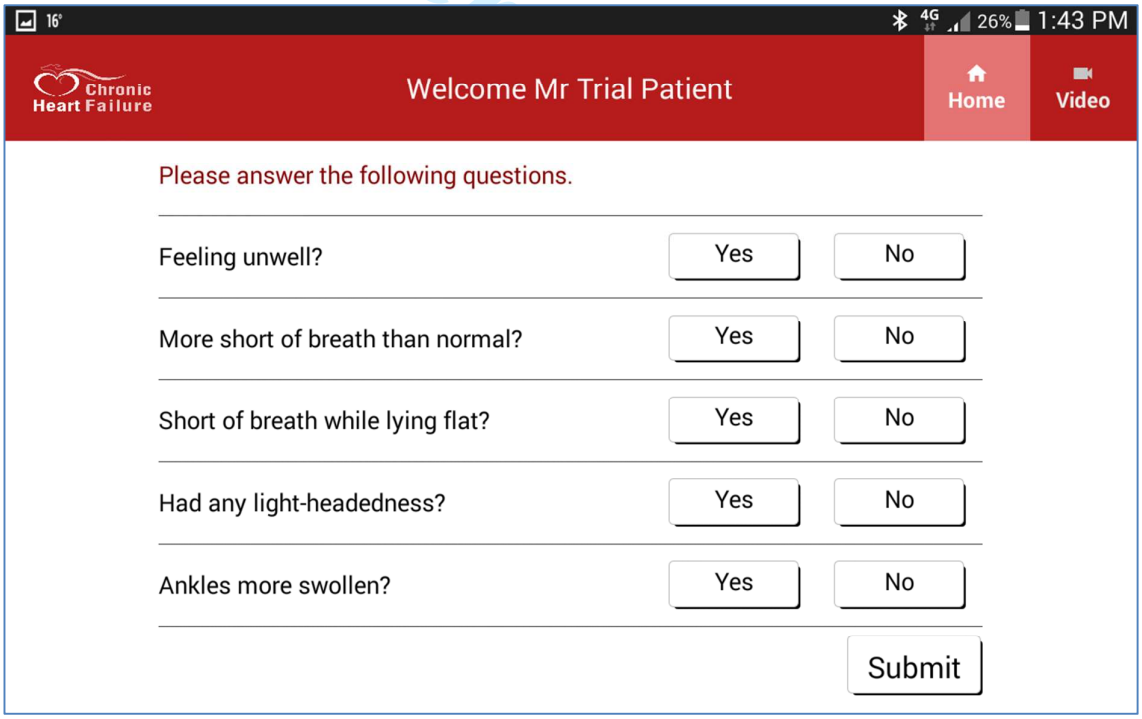
Table 1.

Care Provider	Conditions	Response Time	Interventions
Call Centre (MePACS)	No weight entry detected before 10AM.	In real time, 24 hours, 7 days a week.	Operators at MePACS call the patients to remind them to weigh. If needed, they call nurses to follow-up.
	Technical issues, such as low level of battery power.	In real time, 24 hours, 7 days a week.	Operators at MePACS call the patients to solve the issues, and call nurses to follow-up if needed.
Project Nurses	Fluctuation of 2 kg in 2 days.	In real time, 24 hours, 7 days a week.	Nurses call patients for further assessment and help process the CHF action plan.
	Fluctuation of 5 kg in 28 day (unintentional weight loss / gain)	Work days.	Nurses follow up with the patients, and engage with CHF clinics for further clinical assessments.
	Fluctuation of 1 Kg over 24 hours.	In real time, 24 hours, 7 days a week.	A questionnaire will be automatically triggered on the table to assess clinical symptoms. If the participant has any of the symptoms assessed, the nurses will be notified to follow up with the patient for intervention.

Table 2.

Primary Outcome	
Compliance with daily weight monitoring	Daily weight entries recorded in participant's scale and MMH
Secondary Outcomes	
Other guideline recommendations to the CHF management	Heart Failure Compliance Questionnaire (health maintenance, medication, diet, and exercise)
Health/Clinical Outcomes	Variation of body weight (mean and SD of weekly weight entries)
	Functional capacity (6-minute walk test)
	Health related quality of life (EQ-5D)
	Psychosocial status (CDS, short version)
	Frailty scale (Canadian Frailty Index)
Health Economic Outcomes	Number of hospital readmissions, and length of stay (mean, SD)
	Number of ED visits, and length of stay (mean, SD)
	Number of GP visits

Appendix 1.



CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	4-7
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	3
	2b	Specific objectives or hypotheses	3
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	4
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	n/a
Participants	4a	Eligibility criteria for participants	4
	4b	Settings and locations where the data were collected	4 and 6
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	5
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	6
	6b	Any changes to trial outcomes after the trial commenced, with reasons	n/a
Sample size	7a	How sample size was determined	6
	7b	When applicable, explanation of any interim analyses and stopping guidelines	n/a
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	4
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	4
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	4
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	4
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	4

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	n/a
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	6-7
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	6-7
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	n/a
	13b	For each group, losses and exclusions after randomisation, together with reasons	n/a
Recruitment	14a	Dates defining the periods of recruitment and follow-up	n/a
	14b	Why the trial ended or was stopped	n/a
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	n/a
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	n/a
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	n/a
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	n/a
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	n/a
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	n/a
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	8
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	8
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	8
Other information			
Registration	23	Registration number and name of trial registry	1 and 4
Protocol	24	Where the full trial protocol can be accessed, if available	n/a
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	8

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

BMJ Open

Innovative telemonitoring enhanced care program for chronic heart failure (ITEC-CHF) to improve guideline compliance and collaborative care: protocol of a multicenter randomized controlled trial

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Innovative telemonitoring enhanced care program for chronic heart failure (ITEC-CHF) to improve guideline compliance and collaborative care: protocol of a multicenter randomized controlled trial

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ABSTRACT

Introduction: Chronic heart failure (CHF) is a life-threatening chronic disease characterised by periodic exacerbations and recurrent hospitalisations. In the management of CHF, patient compliance with evidence based clinical guidelines is essential, but remains difficult practically. The objective of this study is to examine whether an innovative telemonitoring enhanced care program for CHF (ITEC-CHF) improves patients' compliance, and associated health and economic outcomes.

Methods and Analysis: An unblinded multicentre randomized controlled trial (RCT) has been designed. Patients will be recruited and randomized to receive either ITEC-CHF (n=150) or usual care (UC-CHF) (n=150) for at least 6 months. ITEC-CHF combines usual care and an additional telemonitoring service including remote weight monitoring, structured telephone support, and nurse-led collaborative care. The primary outcomes are the compliance rates with best-practice guidelines for daily weight monitoring. The secondary outcomes include the compliance with other guideline recommendations (health maintenance, medication, diet, and exercise), health (health related quality of life, risk factors, functional capacity, and psychological states), and economic outcomes (risks of hospital readmission, general practitioner/emergency department visits, and cost benefits).

Ethics and Dissemination: The clinical trial has been approved by Peninsula Health Human Research Ethics Committee (HREC Reference: HREC/14/PH/27), Royal Perth Hospital Human Research Ethics Committee (Reference: 15-081), and the Curtin University Human Research Ethics Committee (Reference: HR 181/2014). We will disseminate the final results to the public via conferences and journal publications. A final study report will also be provided to the ethics committees.

Trial registration: Registered with Australian New Zealand Clinical Trial Registry (Trial ID: ACTRN 12614000916640).

Key words: heart failure, telehealth, internet, compliance

Strength and limitations of this study

1. A multicentre randomized controlled trial to evaluate the effects of telemonitoring on patient compliance with guideline-advocated self-management, and associated clinical outcomes.
2. Special focus on addressing the well-known issue of patient noncompliance with daily weight management.
3. Novel "zero-touch" design to prevent any technical difficulties and weight monitoring burdens to participants.
4. Integration with best-practice clinical workflows and action plan to streamline the intervention processes and minimize the workload to the care providers.
5. The study is limited to a 6-month intervention, potentially insufficient for analysis of long-term effects on patient compliance and health outcomes.

INTRODUCTION

Congestive heart failure (CHF), a life-threatening chronic disease, is a global pandemic[1]. It affects over 26 million people[2] with annual direct costs of over $65 billion globally[3]. Despite advances of modern medicine, patients with CHF continue to experience poor survival (30% to 50% at 5-years[4,5]), debilitating symptoms such as dyspnoea and fatigue[6], poor health related quality of life (HQoL)[7], and episodic clinical exacerbations with high risks of hospitalization[8,9].

To effectively manage CHF, evidence-based guidelines are available internationally[10,11]. A consistent recommendation of guidelines is self-management, such as fluid restrictions and daily weighing to monitor fluid balance[12]. Patient compliance with such clinical guidelines is essential to optimise health outcomes[13], but is often suboptimal[14,15]. For example, 12%-75% of patients in usual care were found to adhere to the cardinal recommendation of daily weighing [15,16]. Noncompliance is likely due to a variety of factors including time constraints[17], insufficient knowledge[18], and limited clinical support[19]. Importantly, patients who are noncompliant with self-management guidelines often fail to effectively engage with clinicians for timely interventions [16] resulting in an increased risks of mortality[20], and hospital readmissions[21,22].

Telemonitoring applications are an evolving strategy to improve CHF care, which have the potential to support patients in self-management[23,24,25]. However the effect of telemonitoring on patient compliance with guideline-advocated self-management has not been extensively studied. To our knowledge, only four RCTs have compared patient compliance between a telemonitoring intervention and usual care group[26,27,28,29]. These trials were limited by small sample sizes (n≤100) or short duration follow-up (≤3 months). Furthermore, their outcomes are inconsistent, with two trials reporting improved patient compliance [26,27] and two reporting no benefit[28,29]. Because of the limited and inconsistent evidence, no meta-analysis studies or reviews have been able to conclude the effectiveness of using telemonitoring to improve patient compliance. These facts highlight the need for further research to substantiate patient compliance in telemonitoring studies for CHF care.

To address the issue of patient noncompliance, we have designed an Innovative Telemonitoring Enhanced Care program for CHF (ITEC-CHF). This program focuses on assisting patients with CHF in complying with the daily weight management recommended by the guidelines. To minimise weight monitoring burdens and technical difficulties, the program proposes a novel "zero-touch" design, meaning that the participants are not required to interact with the technology other than stepping onto a scale for weight measurement as in usual care, and they don't need to learn extra knowledge and skills to receive the telemonitoring intervention. The program is also integrated with existing best-practice clinical workflows and action plan to streamline the intervention and make it seamless for care providers.

To evaluate the program, we will conduct a multicentre RCT. The objective of the trial is to examine the hypothesis that the ITEC-CHF program improves patients' compliance, and associated health and economic outcomes. This trial will examine the patient compliance of an innovative telemonitoring program across different care settings. It will also add essential clinical evidence to support use of telemonitoring applications in the community.

METHOD

Trial design

A prospective unblinded two-arm multicentre RCT has been designed. In the trial, patients with CHF will be recruited at two trial sites: 1) Frankston Hospital and Rosebud Hospital in Victoria (VIC), Australia, and 2) Royal Perth Hospital and Fiona Stanley Hospital in Western Australia (WA).

The participants in the trial will be individually randomized to receive either ITEC-CHF or usual care (UC-CHF) for at least 6 months. The allocation ratio of the randomization is 1:1. The randomization is stratified by the two trial sites (VIC and WA) to ensure the allocation ratio in each site. According to a recommended method[30], a series of random allocation assignments with permuted blocks have been generated, and sealed in opaque envelopes. The block sizes will be kept confidential to prevent potential prediction of the assignments. Data analysts generated the randomization sequence, and will be blinded throughout the trial using de-identified patient data. It will be difficult to effectively blind the participants and care providers to telemonitoring interventions, but we will attempt to avoid unnecessary discussions about the allocations and hypothesized outcomes with the participants and care providers throughout the trial.

The trial flow diagram is presented in Figure 1. Through the trial, project nurses at the trial sites will use their electronic patient administration systems to screen patients with CHF from medical records of patient presentations at the local hospitals and emergency departments. They will also screen patient records at heart failure outpatient clinics, and community healthcare services. The nurses will then record eligible candidates, and accordingly send an invitation letter to the candidates. One week later, project nurses will follow up with the candidates via a telephone call. If a candidate is willing to participate in the trial, the project nurses will arrange a face-to-face interview. During the interview, project nurses will explain the trial processes and requirements in detail, and conduct formal written consent with the candidates who agree to participate in the trial. Participants recruited will be interviewed by the project nurses for a baseline assessment. Each participant will then be randomized into either ITEC-CHF or UC-CHF group. At the 6-month time point, all participants will be assessed again. After the 6-month assessment, if the participants are willing to continue, they can stay in the trial to receive a 12-month assessment. Finally, the project nurses will collect the trial data for the research analysis. Participants will be enrolled from January 2015 to October 2017.

<Figure 1>

Inclusion and exclusion criteria

Patients will be eligible to participate in the trial, if they satisfy all the following inclusion criteria: 1) CHF diagnosed by a clinician with an ejection fraction (EF) ≤40%, 2) able to weigh themselves safely, 3) at least 18 years of age, 4) have a regular personal general practitioner (GP) or agree to use a designated GP, 5) with a permanent residential address, and 6) without significant cognitive impairments. Patients will be excluded if they meet any of the following criteria: a) expected survival < 12 months, such as patients with documented

palliative care in medical records, b) end stage renal failure on dialysis, c) long term nursing home resident, or d) participating in any other clinical trial.

Trial interventions

Usual care

Participants in the UC-CHF group will receive a standard package of paper-based diary and booklets at baseline, including the "Living Well with Chronic Heart Failure" resource produced by the Heart Foundation of Australia (HFA). They will then attend standard CHF clinics and primary care physicians and undertake traditional CHF self-management through the trial period. Each participant will also be provided with an electronic weighing scale (ForaCare, W550, CA, USA), and asked to use the weight scale according to the self-management recommendation of the HFA. Project nurses will visit the participants to download the weight data from the weight scale at scheduled times, approximately every three months.

Enhanced care

The ITEC-CHF program will combine usual care and an additional telemonitoring service. The telemontioring service consists of three major components: remote weight monitoring, structured telephone support, and nurse-led collaborative care. The service is integrated with a telephone call centre (MePACS, VIC, Australia) [31], and a nurse care service according to their workflows in usual care.

The integrated care model of the ITEC-CHF program is shown in Figure 1. In the model, participants are provided with an electronic weighing scale (ForaCare, W550, CA, USA), and a computer tablet (Samsung, Galaxy Tab A, Korea). They are asked to use the scale to measure their body weight daily, immediately after wake-up, following voiding, without shoes, in light clothing, and before the next dose of medication. The measured weight entry is recorded in the scale, and then automatically transmitted to the tablet via a wireless Bluetooth function embedded in the scale. The tablet is preloaded with an Android application (Medtech Global, VIC, Australia). This application receives the weight entry, and uploads the entry to a proprietary software package, called Manage My Health (MMH) (Medtech Global, VIC, Australia). A web application in MMH automatically monitors uploaded weight entries in real time to generate alerts, and triage the alerts to project nurses and the telephone call centre. The rules to generate and triage the alerts are given in Table 1. They were designed in accordance with the HFA guidelines for the prevention, detection and management of CHF in Australia[10].

Operators at the call centre will respond to the alerts in real time (24 hour, 7 days a week). If a participant does not weigh before 10AM, a call operator will call the participant to remind him/her to weigh. During the call, if the participant needs clinical support such as advice for assessing CHF symptoms or managing diet, the call operator will arrange a nurse follow-up. The project nurses will subsequently follow up with the participant via a telephone call or home visit if needed. The call operators also provide technical support through the trial, such as updating the tablet application, and arranging home visits to change batteries in the scales.

The project nurses provide structured interventions according to three types of alerts: rapid weight fluctuation (±2 kg in 2 days), slow weight fluctuation (±5 kg in 28 days), and low-risk weight fluctuation (±1 kg over 24 hours). If a participant has rapid weight fluctuation, a project nurse will be alerted. The nurse will then call the participant to assist him/her in assessing critical symptoms, and activating the CHF action plan if indicated, such as attending their GP, CHF clinic or presenting to an emergency department (ED). For an alert of slow weight fluctuation, the project nurses will assist the participant in assessing CHF symptoms, and arranging clinical review at the participants' GP or CHF clinics. The option to present to an ED may also be applied, if this is clinically indicated. If a participant's body weight fluctuation exceeds ±1 kg (but is less than ±2 kg) over 24 hours, a questionnaire will be automatically triggered and sent to the participant's computer tablet. The user interface of the questionnaire is shown in Appendix 1. If the participant reports any of the clinical conditions in the questionnaire or does not respond to the questionnaire, the project nurses will follow up with the participant for a clinical assessment.

<Figure 2>

Table 1. Alerts generated, and associated interventions provided in the ITEC-CHF program.

Care Provider	Conditions	Response Time	Interventions
Call Centre (MePACS)	No weight entry detected before 10AM.	In real time, 24 hours, 7 days a week.	Operators at MePACS call the patients to remind them to weigh. If needed, they call nurses to follow-up.
	Technical issues, such as low level of battery power.	In real time, 24 hours, 7 days a week.	Operators at MePACS call the patients to solve the issues, and call nurses to follow-up if needed.
Project Nurses	Fluctuation of 2 kg in 2 days.	In real time, 24 hours, 7 days a week.	Nurses call patients for further assessment and help process the CHF action plan.
	Fluctuation of 5 kg in 28 day (unintentional weight loss / gain)	Work days.	Nurses follow up with the patients, and engage with CHF clinics for further clinical assessments.
	Fluctuation of 1 Kg over 24 hours.	In real time, 24 hours, 7 days a week.	A questionnaire will be automatically triggered on the table to assess clinical symptoms. If the participant has any of the symptoms assessed, the nurses will be notified to follow up with the patient for intervention.

Primary and secondary outcomes

The outcome measures of the trial are given in Table 2. The primary outcome will be compliance with daily weight monitoring as evaluated by weight entries, recorded on the electronic scales provided to both the ITEC-CHF and UC-CHF groups. Based on a published study [14], we define that a participant is compliant with daily weight monitoring, if he/she performed weight monitoring at least 4 days a week. The rate of compliant days with weight monitoring (days with at least one body weight entry) per week for each participant during his/her trial period will also be computed; and the histogram of the rate will be analysed. The secondary outcomes will include compliance with other guideline recommendations assessed by Heart Failure Compliance Questionnaire[32] (health maintenance, medication, diet, and exercise), health outcomes including health related

quality of life (EQ-5D[33]), risk factors, functional capacity (6-minute walk test[34]), psychological states (Cardiac Depression Scale, DS-SF2[35]) and frailty scale (Canadian Frailty Index[36]), and health economic outcomes including risks of hospital readmission, and general practitioner/emergency department visits. Patients' characteristics and assessment records will be collected by the project nurses. For evaluation of hospital readmissions and ED presentations, the data will be extracted from electronic patient administration systems of the hospitals in the trial.

Table 2. Trial outcome measures and assessment tools and data resources.

Primary Outcome	
Compliance with daily weight monitoring	Daily weight entries recorded in participant's scale and MMH
Secondary Outcomes	
Other guideline recommendations to the CHF management	Heart Failure Compliance Questionnaire (health maintenance, medication, diet, and exercise)
Health/Clinical Outcomes	Variation of body weight (mean and SD of weekly weight entries)
	Functional capacity (6-minute walk test)
	Health related quality of life (EQ-5D)
	Psychosocial status (CDS, short version)
	Frailty scale (Canadian Frailty Index)
Health Economic Outcomes	Number of hospital readmissions, and length of stay (mean, SD)
	Number of ED visits, and length of stay (mean, SD)
	Number of GP visits

Sample size

Compliance with daily weight monitoring was used to calculate the sample size. The null hypothesis is that the percentage of "compliant" participants in the ITEC-CHF group is not higher than in the UC-CHF group. To reject the null hypothesis, we assumed a compliance rate of 80% in ITEC-CHF, and 65% in UC-CHF. We also assumed an attrition rate of 10%. A two-tailed test with a power of 90% and Alpha of 0.05 was used to calculate the same size to achieve a statistical significance[37]. The power calculation resulted in that the study needs at least 143 participants in each group. Accordingly, we rounded the calculated sample size, and made the trial size of 150 patients in each group, for a total of 300 participants. With this sample size, we have a likelihood of 90% to yield a statistical significance.

Statistical analysis

All participants recruited and randomized into the two trial groups will be included in the final comparative analysis according to the intention-to-treat design. A Chi-square test will be used to compare categorical variables between the ITEC-CHF and UC-CHF group, such as sex, and compliance (compliant patients vs noncompliant patients). ANOVA will be applied to analyse continuous variables such as age and weight variations. A Cox proportional hazards model will be performed to analyse the risks of hospital readmission and ED visits. The analysis will be adjusted for confounding variables including sex, age and trial sites. The confidence interval of 95% will be estimated. A p-value less than 0.05 will be considered as statistical significance for all tests. The statistical analysis will be conducted using SPSSv23. Missing data at the case level will be imputed using a multiple imputation method in the SPSS.

Discussion

Daily weight monitoring is a Class I recommendation in the management of CHF [11] to help maintain fluid balance. Fluid retention is an early sign of acute CHF deterioration, a flag for poor compliance with prescribed medication (especially diuretics) and non-adherence with fluid and salt restrictions. Early identification of abnormal weight fluctuations caused by fluid accumulation allows clinicians to work with the patient to improve their compliance, and provide timely interventions. This potentially reduces the burden of heart failure in terms of reducing preventable hospitalizations and preventing clinical deteriorations amongst patients with CHF [22,38,39].

In usual care, patients often have difficulties using paper based diaries to record daily weight entries, and analyse recorded weight entries in association with observed symptoms in order to seek clinical interventions. Weight monitoring in isolation also requires patients to have the knowledge and skills to effectively identify symptoms, make decisions about their clinical relevance, and act on these. To overcome these difficulties, this study proposes the ITEC-CHF program to automatically detect abnormal weight fluctuations, and provide active clinical support through a call centre and project nurses. Compared with the traditional management of CHF, this program has the potential to dramatically simplify the daily weight monitoring and management, and does not require special knowledge or skills. While engaging with the patients for interventions of abnormal weight fluctuations, the project nurses have opportunities to assess patients' health, and issues of compliance with other recommendations, such as diet, fluid restriction, medication, exercise, and collaborative care. We anticipate that this will allow the nurses to actively engage with patients, and provide a broad range of clinical interventions for the management of CHF. Through the improved compliance and clinical support, it is expected that patients will actively engage with well-established multidisciplinary clinical services for further treatment or care such as titration of diuretic medication.

The efficacy of the program will be evaluated through a multicentre RCT. The evaluation is focused on the improvement in patient compliance and associated outcomes. To accurately evaluate the compliance with daily weight monitoring, objective weight data will be obtained from both intervention and control groups. A validated questionnaire will also be used to assess participant compliance with other important self-management behaviours, as recommended by CHF guidelines [10]. In addition to compliance, the questionnaire will also assess barriers to self-management of CHF more broadly. This will help in the refinement of telemonitoring to support CHF care in future clinical practice.

If the efficacy is validated, use of the ITEC-CHF program will not only improve the patient compliance and health outcomes, but also provide an easy way for care providers to effectively and efficiently engage with patients for collaborative care, especially for patients in rural and remote areas. Based on the ITEC-CHF program, other telemonitoring devices such as ambulatory electrocardiogram, glucose meters and blood pressure monitors can also be easily integrated to provide broader interventions for CHF patients with cardiac conditions and comorbidities including diabetes and hypertension. Therefore, validation of the system for weight compliance would support further exploration of telemonitoring for improving CHF care, as well as other chronic conditions.

The study is limited to the 6-month intervention. The 6-month duration is potentially insufficient to reflect real long-term effects of the program through the ongoing management of CHF. Recent studies, in fact, have already demonstrated an issue of declined patient adherence overtime[40,41]. Therefore, extra caution will be exercised when interpreting the outcomes of this study.

Ethics and dissemination

The ethics application for the trial site in VIC has been approved by Peninsula Health Human Research Ethics Committee (HREC Reference: HREC/14/PH/27), and the ethics applications for Royal Perth Hospital and Fiona Stanley Hospital have been approved by Royal Perth Hospital Human Research Ethics Committee (Reference: 15-081) and the Curtin University Human Research Ethics Committee (Reference: HR 181/2014). The trial has been registered in the Australian New Zealand Clinical Trials Registry (Trial ID: ACTRN12614000916640).

We will report the primary and secondary outcomes regardless of the magnitude and direction of interventional effects or differences between the two trial groups. The report will be disseminated through publication in an appropriate journal, approximately 6 months after finishing data collection.

Author contributions

This study protocol was mainly developed by H.D, A.D, I.E, and R.J. The first draft of the manuscript was written by H.D and R.J. All other authors contributed to design of the clinical study, and/or critical revision of the manuscript.

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Conflicts of interest

We declare that there are no conflicts of interest in the clinical trial.

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<Appendix 1>

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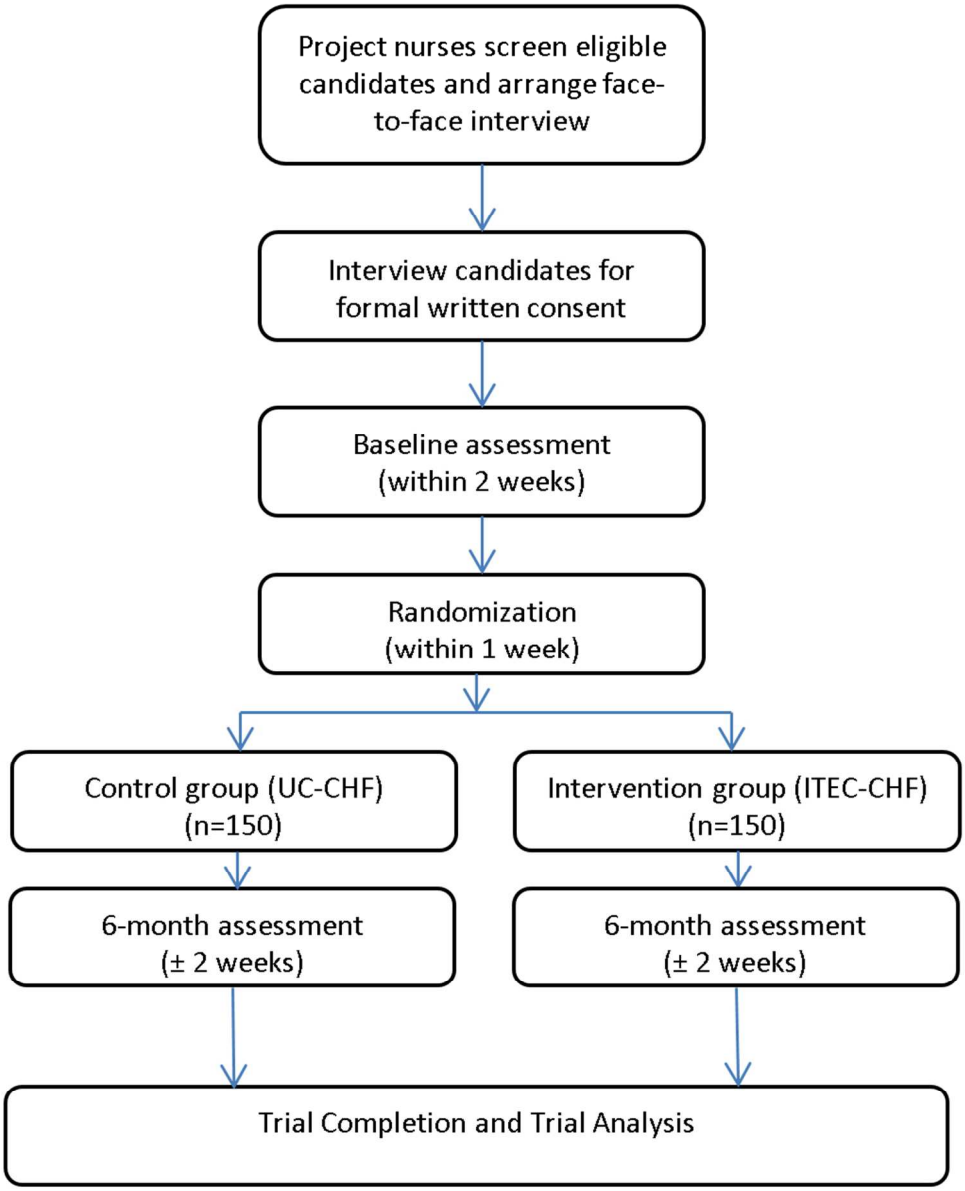

Figure 1. Trial flow diagram of the two-arm randomized controlled trail to compare the ITEC-CHF program with usual care.

87x107mm (300 x 300 DPI)

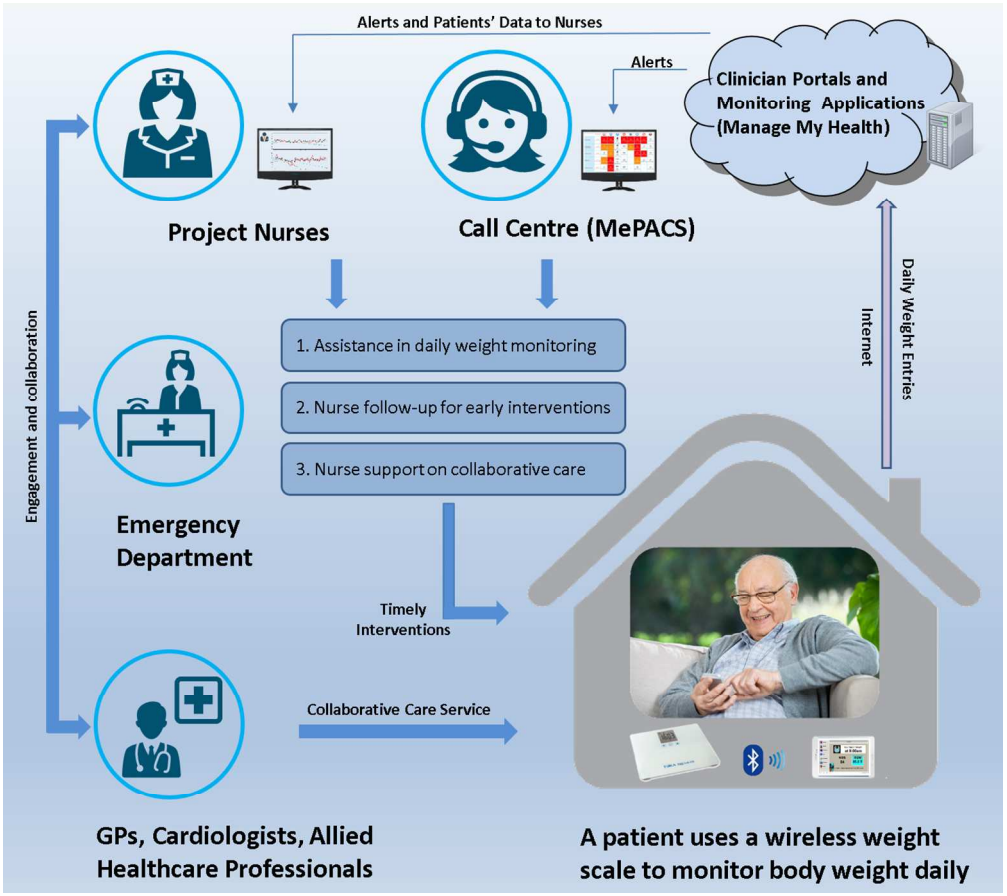

Figure 2. The care model of the ITEC-CHF program is integrated in usual care. The integration includes: 1) remote weight monitoring, 2) structured telephone support, and 3) nurse-led collaborative care.

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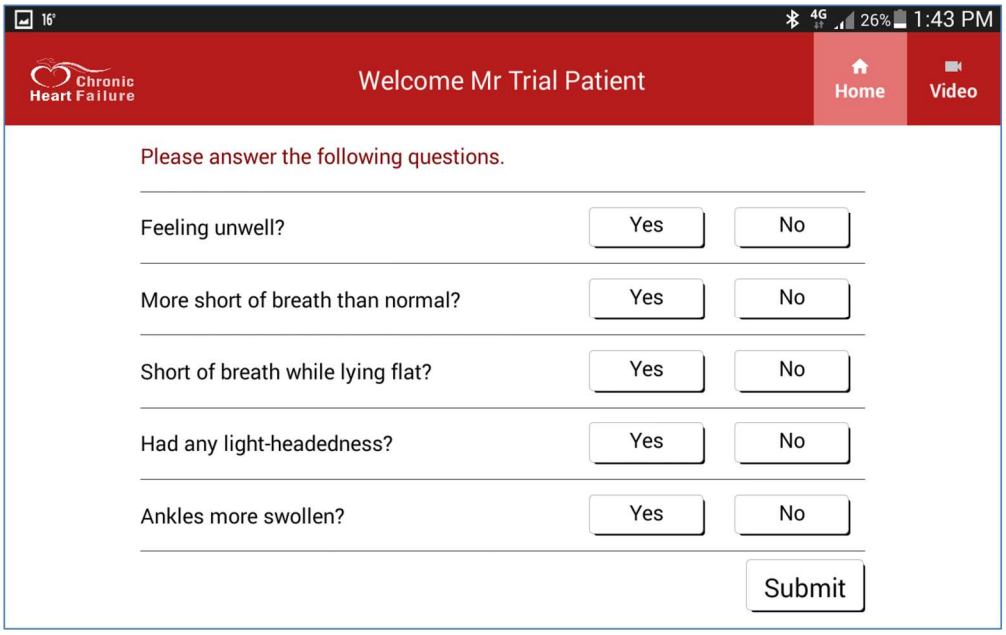

Appendix 1: User interface of the questions sent in the event of a low-level alert.

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BMJ Open

Innovative telemonitoring enhanced care program for chronic heart failure (ITEC-CHF) to improve guideline compliance and collaborative care: protocol of a multicenter randomized controlled trial

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Keywords:	Internet, compliance, telehealth, Heart failure < CARDIOLOGY

Innovative telemonitoring enhanced care program for chronic heart failure (ITEC-CHF) to improve guideline compliance and collaborative care: protocol of a multicenter randomized controlled trial

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ABSTRACT

Introduction: Chronic heart failure (CHF) is a life-threatening chronic disease characterised by periodic exacerbations and recurrent hospitalisations. In the management of CHF, patient compliance with evidence based clinical guidelines is essential, but remains difficult practically. The objective of this study is to examine whether an innovative telemonitoring enhanced care program for CHF (ITEC-CHF) improves patients' compliance, and associated health and economic outcomes.

Methods and Analysis: An open multicentre randomized controlled trial (RCT) has been designed. Patients will be recruited and randomized to receive either ITEC-CHF (n=150) or usual care (UC-CHF) (n=150) for at least 6 months. ITEC-CHF combines usual care and an additional telemonitoring service including remote weight monitoring, structured telephone support, and nurse-led collaborative care. The primary outcomes are the compliance rates with best-practice guidelines for daily weight monitoring. The secondary outcomes include the compliance with other guideline recommendations (health maintenance, medication, diet, and exercise), health (health related quality of life, risk factors, functional capacity, and psychological states), and economic outcomes related to the use of healthcare resources such as hospital readmissions and general practitioner/emergency department visits.

Ethics and Dissemination: The clinical trial has been approved by Peninsula Health Human Research Ethics Committee (HREC Reference: HREC/14/PH/27), Royal Perth Hospital Human Research Ethics Committee (Reference: 15-081), and the Curtin University Human Research Ethics Committee (Reference: HR 181/2014). We will disseminate the final results to the public via conferences and journal publications. A final study report will also be provided to the ethics committees.

Trial registration: Registered with Australian New Zealand Clinical Trial Registry (Trial ID: ACTRN 12614000916640).

Key words: heart failure, telehealth, internet, compliance

Strength and limitations of this study

1. A multicentre randomized controlled trial to evaluate the effects of telemonitoring on patient compliance with guideline-advocated self-management, and associated clinical outcomes.
2. Special focus on addressing the well-known issue of patient noncompliance with daily weight management.
3. Novel "zero-touch" design to prevent any technical difficulties and weight monitoring burdens to participants.
4. Integration with best-practice clinical workflows and action plan to streamline the intervention processes and minimize the workload to the care providers.
5. The study is limited to a 6-month intervention, potentially insufficient for analysis of long-term effects on patient compliance and health outcomes.

Protocol version

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Authors: The research team of the ITECH-CHF study

INTRODUCTION

Congestive heart failure (CHF), a life-threatening chronic disease, is a global pandemic[1]. It affects over 26 million people[2] with annual direct costs of over $65 billion globally[3]. Despite advances of modern medicine, patients with CHF continue to experience poor survival (30% to 50% at 5-years[4,5]), debilitating symptoms such as dyspnoea and fatigue[6], poor health related quality of life (HQoL)[7], and episodic clinical exacerbations with high risks of hospitalization[8,9].

To effectively manage CHF, evidence-based guidelines are available internationally[10,11]. A consistent recommendation of guidelines is self-management, such as fluid restrictions and daily weighing to monitor fluid balance[12]. Patient compliance with such clinical guidelines is essential to optimise health outcomes[13], but is often suboptimal[14,15]. For example, 12%-75% of patients in usual care were found to adhere to the cardinal recommendation of daily weighing [15,16]. Noncompliance is likely due to a variety of factors including time constraints[17], insufficient knowledge[18], and limited clinical support[19]. Importantly, patients who are noncompliant with self-management guidelines often fail to effectively engage with clinicians for timely interventions [16] resulting in an increased risks of mortality[20], and hospital readmissions[21,22].

Telemonitoring applications are an evolving strategy to improve CHF care, which have the potential to support patients in self-management[23,24,25]. However the effect of telemonitoring on patient compliance with guideline-advocated self-management has not been extensively studied. To our knowledge, only four RCTs have compared patient compliance between a telemonitoring intervention and usual care group[26,27,28,29]. These trials were limited by small sample sizes (n≤100) or short duration follow-up (≤3 months). Furthermore, their outcomes are inconsistent, with two trials reporting improved patient compliance [26,27] and two reporting no benefit[28,29]. Because of the limited and inconsistent evidence, no meta-analysis studies or reviews have been able to conclude the effectiveness of using telemonitoring to improve patient compliance. These facts highlight the need for further research to substantiate patient compliance in telemonitoring studies for CHF care.

To address the issue of patient noncompliance, we have designed an Innovative Telemonitoring Enhanced Care program for CHF (ITEC-CHF). This program focuses on assisting patients with CHF in complying with the daily weight management recommended by the guidelines. To minimise weight monitoring burdens and technical difficulties, the program proposes a novel "zero-touch" design, meaning that the participants are not required to interact with the technology other than stepping onto a scale for weight measurement as in usual care, and they don't need to learn extra knowledge and skills to receive the telemonitoring intervention. The program is also integrated with existing best-practice clinical workflows and action plan to streamline the intervention and make it seamless for care providers.

To evaluate the program, we will conduct a multicentre RCT. The objective of the trial is to examine the hypothesis that the ITEC-CHF program improves patients' compliance, and associated health and economic outcomes. This trial will examine the patient compliance of an innovative telemonitoring program across different care settings. It will also add essential clinical evidence to support use of telemonitoring applications in the community.

METHODS

Trial design

A prospective open two-arm multicentre RCT has been designed. In the trial, patients with CHF will be recruited at two trial sites: 1) Frankston Hospital and Rosebud Hospital in Victoria (VIC), Australia, and 2) Royal Perth Hospital and Fiona Stanley Hospital in Western Australia (WA).

The participants in the trial will be individually randomized to receive either ITEC-CHF or usual care (UC-CHF) for at least 6 months. The allocation ratio of the randomization is 1:1. The randomization is stratified by the two trial sites (VIC and WA) to ensure the allocation ratio in each site. According to a recommended method[30], a series of random allocation assignments with permuted blocks have been generated and sealed in opaque envelopes by two research scientists in a research organisation in the study. The block sizes will be kept confidential to prevent potential prediction of the assignments. Data analysts generated the randomization sequence, and will be blinded throughout the trial using de-identified patient data. It will be difficult to effectively blind the participants and care providers to telemonitoring interventions, but we will attempt to avoid unnecessary discussions about the allocations and hypothesized outcomes with the participants and care providers throughout the trial.

The trial flow diagram is presented in Figure 1. Through the trial, project nurses at the trial sites will use their electronic patient administration systems to screen patients with CHF from medical records of patient presentations at the local hospitals and emergency departments. They will also screen patient records at heart failure outpatient clinics, and community healthcare services. The nurses will then record eligible candidates, and accordingly send an invitation letter to the candidates. One week later, project nurses will follow up with the candidates via a telephone call. If a candidate is willing to participate in the trial, the project nurses will arrange a face-to-face interview. During the interview, project nurses will explain the trial processes and requirements in detail, and conduct formal written consent with the candidates who agree to participate in the trial. Participants recruited will be interviewed by the project nurses for a baseline assessment. Each participant will then be randomized into either ITEC-CHF or UC-CHF group. At the 6-month time point, all participants will be assessed again. After the 6-month assessment, if the participants are willing to continue, they can stay in the trial to receive a 12-month assessment. Finally, the project nurses will collect the trial data for the research analysis. Participants will be enrolled from January 2015 to October 2017.

<Figure 1>

Inclusion and exclusion criteria

Patients will be eligible to participate in the trial, if they satisfy all the following inclusion criteria: 1) CHF diagnosed by a clinician with an ejection fraction (EF) ≤40%, 2) able to weigh themselves safely, 3) at least 18 years of age, 4) have a regular personal general practitioner (GP) or agree to use a designated GP, 5) with a permanent residential address, and 6) without significant cognitive impairments. Patients will be excluded if they meet any of the following criteria: a) expected survival < 12 months, such as patients with documented

palliative care in medical records, b) end stage renal failure on dialysis, c) long term nursing home resident, or d) participating in any other clinical trial.

Trial interventions

Usual care

Participants in the UC-CHF group will receive a standard package of paper-based diary and booklets at baseline, including the "Living Well with Chronic Heart Failure" resource produced by the Heart Foundation of Australia (HFA). They will then attend standard CHF clinics and primary care physicians and undertake traditional CHF self-management through the trial period. Each participant will also be provided with an electronic weighing scale (ForaCare, W550, CA, USA), and asked to use the weight scale according to the self-management recommendation of the HFA. Project nurses will visit the participants to download the weight data from the weight scale at scheduled times, approximately every three months.

Enhanced care

The ITEC-CHF program will combine usual care and an additional telemonitoring service. The telemontioring service consists of three major components: remote weight monitoring, structured telephone support, and nurse-led collaborative care. The service is integrated with a telephone call centre (MePACS, VIC, Australia) [31], and a nurse care service according to their workflows in usual care.

The integrated care model of the ITEC-CHF program is shown in Figure 2. In the model, participants are provided with an electronic weighing scale (ForaCare, W550, CA, USA), and a computer tablet (Samsung, Galaxy Tab A, Korea). They are asked to use the scale to measure their body weight daily, immediately after wake-up, following voiding, without shoes, in light clothing, and before the next dose of medication. The measured weight entry is recorded in the scale, and then automatically transmitted to the tablet via a wireless Bluetooth function embedded in the scale. The tablet is preloaded with an Android application (Medtech Global, VIC, Australia). This application receives the weight entry, and uploads the entry to a proprietary software package, called Manage My Health (MMH) (Medtech Global, VIC, Australia). A web application in MMH automatically monitors uploaded weight entries in real time to generate alerts, and triage the alerts to project nurses and the telephone call centre. The rules to generate and triage the alerts are given in Table 1. They were designed in accordance with the HFA guidelines for the prevention, detection and management of CHF in Australia[10].

Operators at the call centre will respond to the alerts in real time (24 hour, 7 days a week). If a participant does not weigh before 10AM, a call operator will call the participant to remind him/her to weigh. During the call, if the participant needs clinical support such as advice for assessing CHF symptoms or managing diet, the call operator will arrange a nurse follow-up. The project nurses will subsequently follow up with the participant via a telephone call or home visit if needed. The call operators also provide technical support through the trial, such as updating the tablet application, and arranging home visits to change batteries in the scales.

The project nurses provide structured interventions according to three types of alerts: rapid weight fluctuation (±2 kg in 2 days), slow weight fluctuation (±5 kg in 28 days), and low-risk weight fluctuation (±1 kg over 24 hours). If a participant has rapid weight fluctuation, a project nurse will be alerted. The nurse will then call the participant to assist him/her in assessing critical symptoms, and activating the CHF action plan if indicated, such as attending their GP, CHF clinic or presenting to an emergency department (ED). For an alert of slow weight fluctuation, the project nurses will assist the participant in assessing CHF symptoms, and arranging clinical review at the participants' GP or CHF clinics. The option to present to an ED may also be applied, if this is clinically indicated. If a participant's body weight fluctuation exceeds ±1 kg (but is less than ±2 kg) over 24 hours, a questionnaire will be automatically triggered and sent to the participant's computer tablet. The user interface of the questionnaire is shown in Appendix 1. If the participant reports any of the clinical conditions in the questionnaire or does not respond to the questionnaire, the project nurses will follow up with the participant for a clinical assessment.

<Figure 2>

Table 1. Alerts generated, and associated interventions provided in the ITEC-CHF program.

Care Provider	Conditions	Response Time	Interventions
Call Centre (MePACS)	No weight entry detected before 10AM.	In real time, 24 hours, 7 days a week.	Operators at MePACS call the patients to remind them to weigh. If needed, they call nurses to follow-up.
	Technical issues, such as low level of battery power.	In real time, 24 hours, 7 days a week.	Operators at MePACS call the patients to solve the issues, and call nurses to follow-up if needed.
Project Nurses	Fluctuation of 2 kg in 2 days.	In real time, 24 hours, 7 days a week.	Nurses call patients for further assessment and help process the CHF action plan.
	Fluctuation of 5 kg in 28 day (unintentional weight loss / gain)	Work days.	Nurses follow up with the patients, and engage with CHF clinics for further clinical assessments.
	Fluctuation of 1 Kg over 24 hours.	In real time, 24 hours, 7 days a week.	A questionnaire will be automatically triggered on the table to assess clinical symptoms. If the participant has any of the symptoms assessed, the nurses will be notified to follow up with the patient for intervention.

Primary and secondary outcomes

The outcome measures of the trial are given in Table 2. The primary outcome will be compliance with daily weight monitoring as evaluated by weight entries, recorded on the electronic scales provided to both the ITEC-CHF and UC-CHF groups. Based on a published study [14], we define that a participant is compliant with daily weight monitoring, if he/she performed weight monitoring at least 4 days a week. The rate of compliant days with weight monitoring (days with at least one body weight entry) per week for each participant during his/her trial period will also be computed; and the histogram of the rate will be analysed. The secondary outcomes will include compliance with other guideline recommendations assessed by Heart Failure Compliance Questionnaire[32] (health maintenance, medication, diet, and exercise), health outcomes including health related

quality of life (EQ-5D[33]), risk factors, functional capacity (6-minute walk test[34]), psychological states (Cardiac Depression Scale, DS-SF2[35]) and frailty scale (Canadian Frailty Index[36]), and health economic outcomes related to the use of healthcare resources such as hospital readmissions and general practitioner/emergency department visits. Patients' characteristics and assessment records will be collected by the project nurses. For evaluation of hospital readmissions and ED presentations, the data will be extracted from electronic patient administration systems of the hospitals in the trial.

Table 2. Trial outcome measures and assessment tools and data resources.

Primary Outcome	
Compliance with daily weight monitoring	Daily weight entries recorded in participant's scale and MMH
Secondary Outcomes	
Other guideline recommendations to the CHF management	Heart Failure Compliance Questionnaire (health maintenance, medication, diet, and exercise)
Health/Clinical Outcomes	Variation of body weight (mean and SD of weekly weight entries)
	Functional capacity (6-minute walk test)
	Health related quality of life (EQ-5D)
	Psychosocial status (CDS, short version)
	Frailty scale (Canadian Frailty Index)
Health Economic Outcomes	Number of hospital readmissions, and length of stay (mean, SD)
	Number of ED visits, and length of stay (mean, SD)
	Number of GP visits

Strategies of participant retention

Prior to the trial recruitment, we will discuss the importance of participant retention within the recruitment and care teams. During the trial, each participant recruited will be provided with a telephone contact in the information package. Through the contact, the participants can contact project nurses for trial-related support. A structured procedure will be in place to guide project nurses to document the participants' enquiries, and ensure timely responses and/or follow-ups. Moreover, the project nurses will visit each participant every 3 months, to discuss any concerns or issues related to the trial and change the batteries in the weight scale.

Participant discharge

Participants will be discharged from the trial under the conditions of 1) mortality, 2) elective withdrawal, and 3) full completion of the program. When discharging participants, projects nurses will document the conditions in case report forms (CRF) with date and causes in detail.

Data security and storage

All trial files, including the master list, CRF, and clinical assessment forms, will be stored securely, either in password-protected computer files or in locked filing cabinets in a secure area at Peninsula Health or Curtin University. Access to these files will only be granted to study personnel trained in confidentiality and privacy

procedures at the hospitals in the study. All trial data provided for research analysis will be de-identified, including patient characteristics, primary and secondary outcomes, and data entries through the healthcare and telemonitoring systems in the study.

All the trial files and data will be stored securely for a minimum of 5 years after completion of the study and, finally, be securely destroyed according to Privacy Policy provided by the National Health and Medical Research Council of Australia.

Sample size

Compliance with daily weight monitoring was used to calculate the sample size. The null hypothesis is that the percentage of "compliant" participants in the ITEC-CHF group is not higher than in the UC-CHF group. To reject the null hypothesis, we assumed a compliance rate of 80% in ITEC-CHF, and 65% in UC-CHF. We also assumed an attrition rate of 10%. A two-tailed test with a power of 90% and Alpha of 0.05 was used to calculate the same size to achieve a statistical significance[37]. The power calculation resulted in that the study needs at least 143 participants in each group. Accordingly, we rounded the calculated sample size, and made the trial size of 150 patients in each group, for a total of 300 participants. With this sample size, we have a likelihood of 90% to yield a statistical significance.

Statistical analysis

All participants recruited and randomized into the two trial groups will be included in the final comparative analysis according to the intention-to-treat design. A Chi-square test will be used to compare categorical variables between the ITEC-CHF and UC-CHF group, such as sex, and compliance (compliant patients vs noncompliant patients). ANOVA will be applied to analyse continuous variables such as age and weight variations. A Cox proportional hazards model will be performed to analyse the risks of hospital readmission and ED visits. The analysis will be adjusted for confounding variables including sex, age and trial sites. The confidence interval of 95% will be estimated. A p-value less than 0.05 will be considered as statistical significance for all tests. The statistical analysis will be conducted using SPSSv23. Missing data at the case level will be imputed using a multiple imputation method in the SPSS.

Trial management

A Project Working Group (PWG) will be composed of the chief investigators, research scientists or project managers from the organizations of the project. The PWG will convene monthly (with additional meetings if needed) and take overall responsibility for the conduct of the trial, such as managing the trial progress, reviewing adverse events in CRF, resolving technical issues, and monitoring trial data. If necessary, the committee will advise and make changes in the clinical trial protocol. The PWG will be independent from project sponsors and free from competing interests.

A project control board (PCB) will be composed of a) CHF clinical champions, b) chief investigators, c) researchers, and d) project managers. The PCB will convene monthly to govern the project and ensure that the project meets all requirements outlined in the project plan. The major responsibilities of the PCB will include 1)

reviewing the study plan, 2) providing reports to the project sponsors and ethics committees, 3) deciding budget and administration, 4) resolving contractual issues, and 5) maintaining IT and telemonitoring systems in the trial. The PCB will also work with independent management committees for safety and quality of care at corresponding hospitals, to assess the severity of incidents and adverse effects. The PCB will have the capacity to terminate the trial in the event of slow recruitment, safety concerns, or overwhelming evidence of benefit.

A Clinical Trial Advisory Committee, composed of chief investigators and research scientists, will convene monthly. The committee will implement and maintain quality assurance and quality control systems to ensure the trial in compliance with the protocol and applicable policies. The committee will also arrange at least one audit during the trial. An arranged audit team will check the overall quality and completeness of the data, examine source documents, and ensure that the trial complies with the requirements outlined by the trial protocol, ethics applications and hospital policies. The audit process will be independent from chief investigators and project sponsors. Discussion

Daily weight monitoring is a Class I recommendation in the management of CHF [11] to help maintain fluid balance. Fluid retention is an early sign of acute CHF deterioration, a flag for poor compliance with prescribed medication (especially diuretics) and non-adherence with fluid and salt restrictions. Early identification of abnormal weight fluctuations caused by fluid accumulation allows clinicians to work with the patient to improve their compliance, and provide timely interventions. This potentially reduces the burden of heart failure in terms of reducing preventable hospitalizations and preventing clinical deteriorations amongst patients with CHF [22,38,39].

In usual care, patients often have difficulties using paper based diaries to record daily weight entries, and analyse recorded weight entries in association with observed symptoms in order to seek clinical interventions. Weight monitoring in isolation also requires patients to have the knowledge and skills to effectively identify symptoms, make decisions about their clinical relevance, and act on these. To overcome these difficulties, this study proposes the ITEC-CHF program to automatically detect abnormal weight fluctuations, and provide active clinical support through a call centre and project nurses. Compared with the traditional management of CHF, this program has the potential to dramatically simplify the daily weight monitoring and management, and does not require special knowledge or skills. While engaging with the patients for interventions of abnormal weight fluctuations, the project nurses have opportunities to assess patients' health, and issues of compliance with other recommendations, such as diet, fluid restriction, medication, exercise, and collaborative care. We anticipate that this will allow the nurses to actively engage with patients, and provide a broad range of clinical interventions for the management of CHF. Through the improved compliance and clinical support, it is expected that patients will actively engage with well-established multidisciplinary clinical services for further treatment or care such as titration of diuretic medication.

The efficacy of the program will be evaluated through a multicentre RCT. The evaluation is focused on the improvement in patient compliance and associated outcomes. To accurately evaluate the compliance with daily weight monitoring, objective weight data will be obtained from both intervention and control groups. A validated questionnaire will also be used to assess participant compliance with other important self-management behaviours, as recommended by CHF guidelines [10]. In addition to compliance, the questionnaire will also assess

barriers to self-management of CHF more broadly. This will help in the refinement of telemonitoring to support CHF care in future clinical practice.

If the efficacy is validated, use of the ITEC-CHF program will not only improve the patient compliance and health outcomes, but also provide an easy way for care providers to effectively and efficiently engage with patients for collaborative care, especially for patients in rural and remote areas. Based on the ITEC-CHF program, other telemonitoring devices such as ambulatory electrocardiogram, glucose meters and blood pressure monitors can also be easily integrated to provide broader interventions for CHF patients with cardiac conditions and comorbidities including diabetes and hypertension. Therefore, validation of the system for weight compliance would support further exploration of telemonitoring for improving CHF care, as well as other chronic conditions.

The study is limited to the 6-month intervention. The 6-month duration is potentially insufficient to reflect real long-term effects of the program through the ongoing management of CHF. Recent studies, in fact, have already demonstrated an issue of declined patient adherence overtime[40,41]. Therefore, extra caution will be exercised when interpreting the outcomes of this study.

Ethics and dissemination

The ethics application for the trial site in VIC has been approved by Peninsula Health Human Research Ethics Committee (HREC Reference: HREC/14/PH/27), and the ethics applications for Royal Perth Hospital and Fiona Stanley Hospital have been approved by Royal Perth Hospital Human Research Ethics Committee (Reference: 15-081) and the Curtin University Human Research Ethics Committee (Reference: HR 181/2014). The trial has been registered in the Australian New Zealand Clinical Trials Registry (Trial ID: ACTRN12614000916640).

We will report the primary and secondary outcomes regardless of the magnitude and direction of interventional effects or differences between the two trial groups. The report will be disseminated through publication in an appropriate journal, approximately 6 months after finishing data collection.

Figure Legends:

Figure 1. Trial flow diagram of the two-arm randomized controlled trail to compare the ITEC-CHF program with usual care.

Figure 2. The care model of the ITEC-CHF program is integrated within usual care. The integration includes: 1) remote weight monitoring, 2) structured telephone support, and 3) nurse-led collaborative care.

Appendix 1: User interface of the questions to the patient in the event of a low-level alert.

Author contributions

This study protocol was mainly developed by H.D, A.D, I.E, and R.J. The first draft of the manuscript was written by H.D and R.J. All other authors contributed to design of the clinical study, and/or critical revision of the manuscript.

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Conflicts of interest

We declare that there are no conflicts of interest in the clinical trial.

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<Appendix 1>

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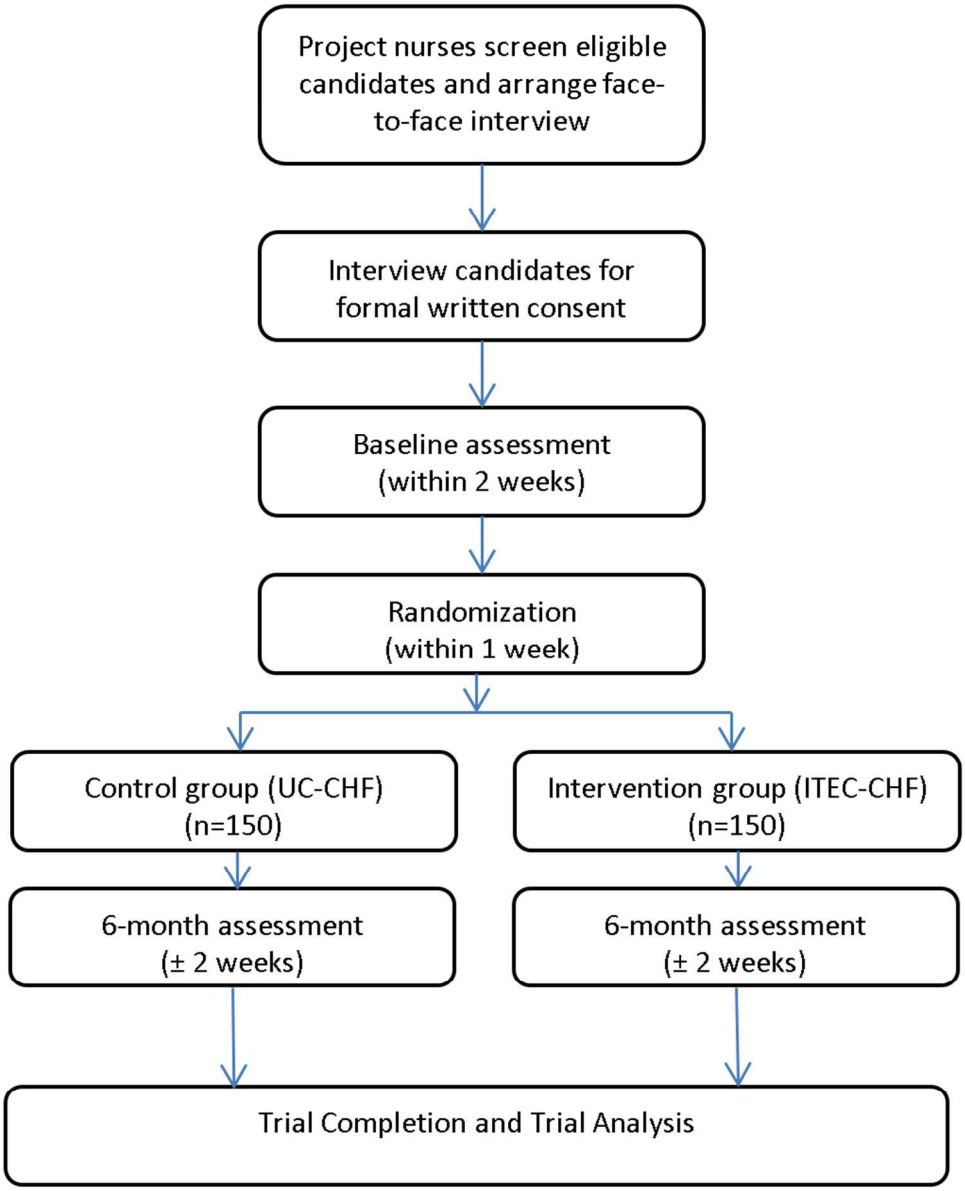


Figure 1. Trial flow diagram of the two-arm randomized controlled trail to compare the ITEC-CHF program with usual care.

87x107mm (300 x 300 DPI)

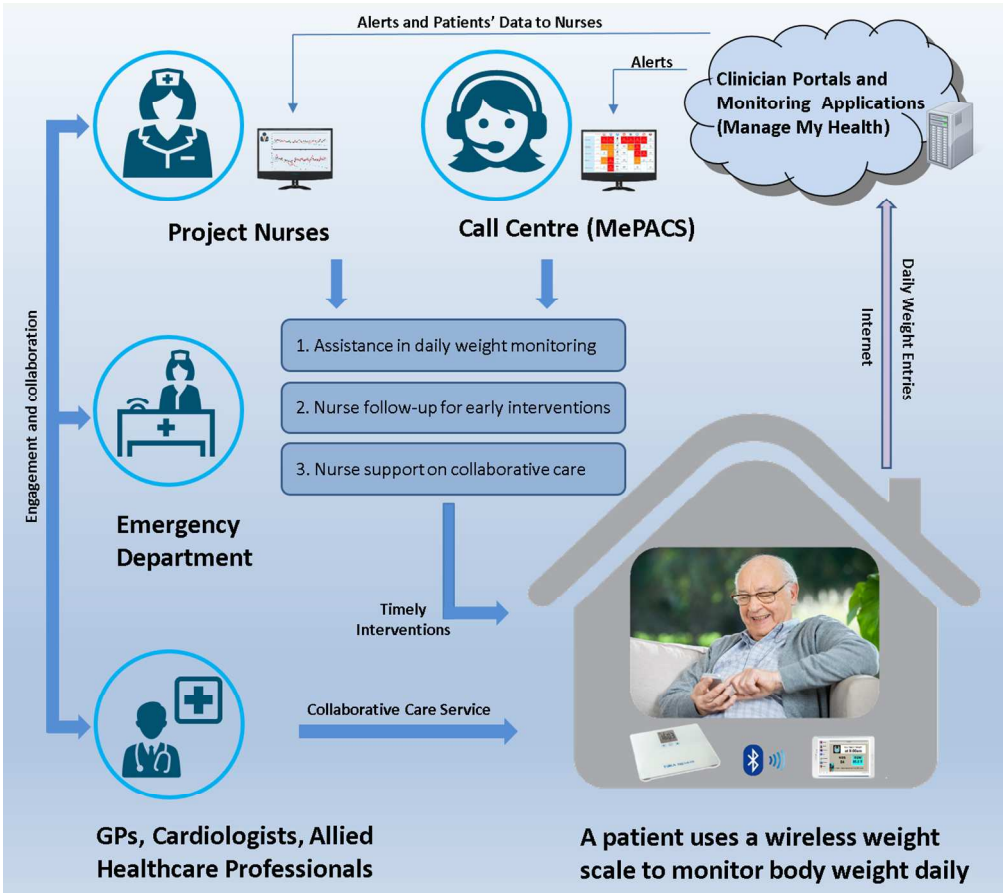
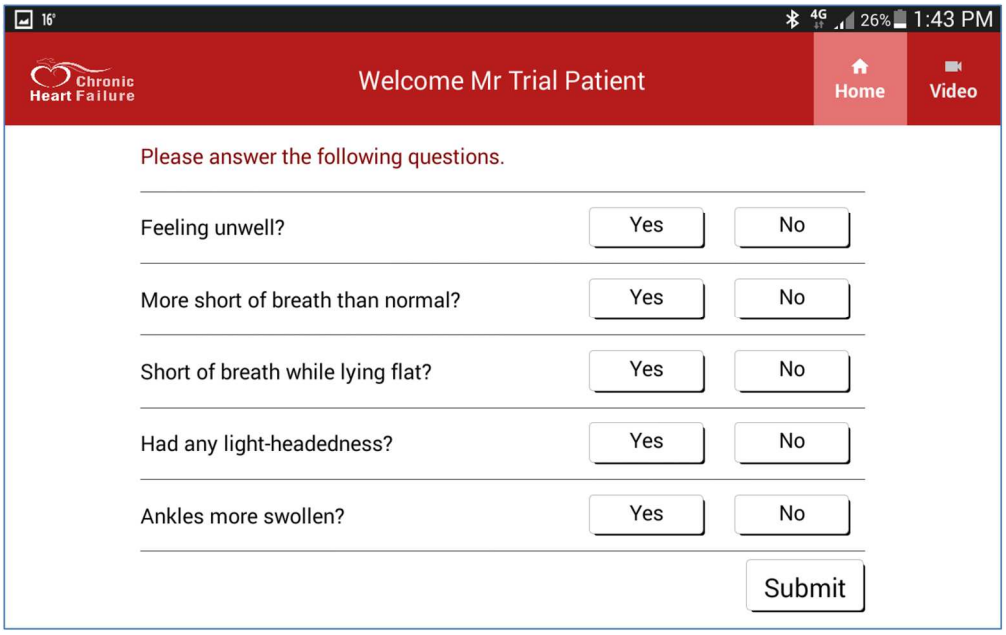


Figure 2. The care model of the ITEC-CHF program is integrated in usual care. The integration includes: 1) remote weight monitoring, 2) structured telephone support, and 3) nurse-led collaborative care.

124x110mm (300 x 300 DPI)



Appendix 1: User interface of the questions to the patient in the event of a low-level alert.

160x100mm (300 x 300 DPI)

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	_____1_____
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	_____2_____
	2b	All items from the World Health Organization Trial Registration Data Set	__2(ANZCTR)__
Protocol version	3	Date and version identifier	_____2_____
Funding	4	Sources and types of financial, material, and other support	_____11_____
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	____1,10_____
	5b	Name and contact information for the trial sponsor	_____11_____
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	_____11_____
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	_____8_____

Introduction

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3
	6b	Explanation for choice of comparators	3
Objectives	7	Specific objectives or hypotheses	3
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	4

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	4
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	4,5
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	5,6
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	7
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	n/a
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	n/a
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	6,7
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	4

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	8
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	4
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	4
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	4
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	4
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	4
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	6
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	7

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	7,8
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	8
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	8
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	6
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	8,9
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	9
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	8
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	9
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	2
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	8

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	4
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	4,8
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	11
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	8
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	2
	31b	Authorship eligibility guidelines and any intended use of professional writers	n/a
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	2
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	4
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.