Trial Title: Home monitoring with integrated risk-stratified disease management support versus home monitoring alone in patients with heart failure: a randomised controlled trial

Trial Acronym: SUPPORT-HF 2 (Seamless User-centred Proactive Provision Of Risk-stratified Treatment for Heart Failure)

Ethics Ref: 14/SS/1025

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Chief Investigator Signature:

Confidentiality Statement

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, host organisation, and members of the Research Ethics Committee, unless authorised to do so.

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2 KEY TRIAL CONTACTS

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3 SYNOPSIS

Trial title	Home monitoring with integrated risk-stratified disease management support versus home monitoring alone in patients with heart failure to optimise the use of medical therapy: a randomised controlled trial
Acronym	SUPPORT-HF 2
Rationale	The provision of evidence-based care to heart failure patients is a major challenge to health systems worldwide. It has been suggested that systems of care that enable patients and their carers to monitor and manage their own health - in particular when supported by healthcare professionals remotely - may improve patient outcomes and reduce healthcare utilisation. We are currently completing the SUPPORT-HF 1 study, in which 58 patients with heart failure provided rich qualitative and quantitative insights as to how to develop and sustain a simple and user-friendly system that allows reliable remote communication with a range of heart failure patients. Preliminary results from this study suggest that patients are willing to adopt the SUPPORT-HF remote monitoring system and may benefit from the reassurance it provides. This study aims to assess the preliminary effectiveness of such an IT-supported disease management system.

Hypothesis	In patients with heart failure, home monitoring coupled with an integrated data analysis and risk prediction service, providing real-time alerts and advice to patients and predictive clinical decision support tools to healthcare practitioners, is more effective in optimising medical therapy than home monitoring with the same monitoring equipment but without the use of the integrated data analysis and decision support service and the tailored self-management tools.	
Trial design	A multicentre two-armed partially blinded parallel randomised controlled trial	
Trial participants	Adults with confirmed diagnosis of heart failure (irrespective of the underlying aetiology) who have the potential to benefit from home monitoring and management (defined as self-assessed NYHA class II-IV, or elevated BNP / NT-pro-BNP; AND either not on optimal medical therapy, or at high risk of death within the next year, or at least one hospitalisation in the past 12 months). Patients who in the opinion of the Investigator are unsuitable for participation, and those without any reliable 3G mobile or WiFi network connectivity at home will be excluded. Participating study sites will need to have the capacity for integration of home monitoring data with NHS data, to capture test results and drug prescriptions.	
Planned sample size	200	
Recruitment duration	9 months	
Intervention duration	6 months	
Follow-up duration	Until end of trial	
Planned trial period	September 2014 to December 2015	
Setting	United Kingdom. Recruitment will be from hospitals or outpatient clinics. The study will take place in the community (most of the use of the system will be in the participants' home).	
	Objectives	Outcome Measures/Endpoints
Primary	To investigate whether, in patients with heart failure, an integrated data acquisition, data analysis and risk prediction service capable of providing real-time alerts and advice to patients and predictive clinical decision support tools to healthcare practitioners leads to a **greater increase in the use of recommended medical therapy** than home monitoring with the same monitoring equipment but without the use of the integrated and personalized data analysis and decision support system.	Optimal medical therapy is defined as treatment consistent with the NICE guidelines for management of patients with chronic heart failure and will be measured as a composite opportunity score.
Secondary	To investigate whether participants in the intervention arm achieve **higher levels of physical well---being** than those in the control arm	Physical functioning domain of the Minnesota Living with Heart Failure questionnaire and changes to self-assessed NYHA class

	To investigate whether participants in the intervention arm achieve **lower levels of risk of adverse outcomes** than those in the control arm	Changes to the validated MAGGIC risk score and changes to blood BNP/ NT-pro-BNP
Tertiary	To investigate the safety of IT-supported drug management	Composite of cardiovascular death, cardiovascular admissions (including renal failure and hypotensive episodes) and unscheduled outpatient visits
	To estimate adherence with home monitoring system	The proportion of participants' who discontinue monitoring before the end of study
	To estimate resource utilization	Recruitment rate, intervention and service utilization costs
	Supported Medical Management arm	**Enhanced Self---Management arm**
Intervention	Collection of symptoms, physiological and system usage information from commercially available home monitoring devices (tablet computer, Bluetooth-enabled blood pressure and heart rate monitor and weighing scale) and their integration with electronic health records (EHRs) for estimation of fluid status and risk. Risk-based algorithmic management supported by a specialist medical team and computer algorithms (personalised self-management support and automated feedback to patients for adherence management and change in diuretic dose; individualised specialist treatment advice to patients and their GPs for safety blood testing and changes in drug management).	Collection of symptoms, physiological and system usage information from commercially available home monitoring devices, as well as biochemical data from EHRs, but the data collected will not processed to provide personalised feedback to patients for self-management or to their doctors for risk-based monitoring or drug management. Participants' pharmacological care will not be supported by the system.
Expected outcome	This will be the first trial of a 'third-generation' remote monitoring system using commercially available devices which are expected to become available at low cost and enhances these with customised applications to predict risk and advise on management at scale. The finding of this study on its own has the potential to change medical practice but we aim to build on the study findings to design and conduct a large-scale trial of more than 1000 patients, which could potentially have transformative effects on integrated digital health management worldwide.	

4 ABBREVIATIONS

ARO	Academic Research Organisation
BNP	Brain-natriuretic peptide

CI	Chief Investigator
CRF	Case Report Form
CTRG	Clinical Trials and Research Governance
EHR	Electronic Health Records
GCP	Good Clinical Practice
GP	General Practitioner
ICF	Informed Consent Form
ICH	International Conference of Harmonisation
IRB	Independent Review Board
MAGGIC	Meta-Analysis Global Group in Chronic Heart Failure
NHFA	National Heart Failure Audit
NHS	National Health Service
NRES	National Research Ethics Service
PI	Principal Investigator
PIL	Participant/ Patient Information Leaflet/Letter
R&D	NHS Trust R&D Department
REC	Research Ethics Committee
SAE	Serious Adverse Event
SOP	Standard Operating Procedure

5 BACKGROUND AND RATIONALE

Heart failure is a common and costly condition. Although there is some evidence to suggest modest declines in age-specific prevalence and rates of hospitalisation for heart failure, its burden to patients and health services remains substantial. According to the National Heart Failure Audit (NHFA) report, about half of all hospitalised heart failure patients die or are readmitted to hospital within a year after discharge.[1] These poor patient outcomes are likely to be at least partly explained by underuse of evidence-based therapies and shortcomings of our healthcare delivery systems to provide high-quality care for this large patient population. For example, in a recent analysis of the NHFA we showed that hospital-level prescription of three classes of evidence-based medications ranged from 33% to 76% among 176 hospitals in England and Wales and this variation, which persisted after case-mix adjustment, was strongly associated with mortality early after discharge (publication in preparation). While it is commonly expected that drug management will be optimised after discharge from hospital, evidence suggests that this may not be the case. In fact, one study that evaluated the use of beta-blockers across a range of cardiovascular conditions in general practice found that prescription rates for these drugs actually dropped by over 25% a year after the initial diagnosis.[2]

Several studies have investigated the reasons for the wide and persistent gaps between evidence and practice. For example, a recent survey of UK healthcare professionals involved in heart failure care reported that physicians and nurses often feel overloaded with information from the increasingly

voluminous clinical practice guidelines. They perceive disease management for this multi-morbid patient population complex and are often uncertain about how to deal with the apparent unpredictability of their heart failure patients' disease course. Furthermore, they do not have sufficient time and human resources required for frequent monitoring for drug titration and safety checks.[3]

In theory, innovative models of care delivery that make better use of technological advances, in particular information and communication technology (ICT) are ideally suited to help overcome many of these barriers.[4] Remote data capture, processing and communication systems enable more frequent monitoring at lower cost per unit of information processed. The system can improve the accuracy of estimating risk based on individual's profile and population-level risks. It can synthesise and standardise some of the specialist knowledge, and tailor treatment recommendations according to the patient profile. Furthermore, it can provide a scalable platform for patient education and communication, so that their preferences for alternative treatment strategies can be adequately considered. By reducing the frequency of unnecessary face-to-face interactions with healthcare professionals, such systems are likely to provide a more sustainable and affordable alternative to the prevailing labour-intensive models of care for heart failure patients.

However, despite the intuitive appeal of such systems, the evidence for their effectiveness, cost-effectiveness and sustainability is inconsistent.[5–7] Most randomised trials to date that have shown a beneficial effect have been based on single-centre specialist centres or included only small numbers of highly selected patient populations with optimistic effect estimations. On the other hand, some of the largest studies have had rather disappointing outcomes.[8,9] Consequently, the latest European Society of Cardiology (ESC) guidelines (2012), and the National Institute for Clinical Excellence (NICE) guidelines, conclude that current evidence for the use of remote monitoring systems is insufficiently robust to support a guideline recommendation. They emphasise the need for further studies to evaluate the longterm efficacy and safety of such systems.[10,11]

How to best design and evaluate service delivery interventions in the complex and dynamic environment of healthcare delivery for heart failure (and other chronic diseases) has been subject to much debate.[12] We believe that for ICT-supported chronic disease management systems to replace the prevailing labour-intensive models of care, the intervention itself needs to meet six essential requirements. It must (1) demonstrate wide consumer acceptability and engagement,[13] (2) allow integration into existing clinical pathways, (3) provide accurate early prediction of risk for timely intervention,[5,14] (4) support clinical decision-making with minimal delays in response to abnormal signals,[6] (5) enable systematic management of substantially larger patients than current systems can afford, (6) and be clinically effective. Preliminary results from the SUPPORT-HF 1 study indicate that we are close to meeting the first two requirements listed above: Demonstrating the usability of a low-cost, user-centered, adaptive, integrated digital health platform. SUPPORT-HF 2 now aims to address the next three requirements for large-scale remote management of patients with heart failure.

However, the development of the intervention platform on its own will not be sufficient for demonstrating clinically important but likely modest differences in healthcare outcomes and resource utilization. The evaluation of the intervention must allow sufficient flexibility of the intervention to iteratively adapt to the changing environments (e.g., availability of new technologies) without loosing the value of randomised experiments which are ideally suited for detecting modest causal differences.[12] Finally, the context into which an intervention is to be introduced may determine the ultimate success or

failure of the intervention. Integrated digital health care is likely to be most useful in contexts where quality of care is poor on average with substantial unwarranted variability at the provider-level.[15]

SUPPORT-HF 2 has been designed with particular consideration of these technological, procedural and contextual requirements.

6 OBJECTIVES AND OUTCOME MEASURES

The overall aim of the SUPPORT-HF research programme is to develop an integrated, patient-centred, affordable and sustainable system for proactive heart failure management based on patients' needs using innovative technologies and methodologies for service design. The specific objectives and outcomes measures of the SUPPORT-HF 2 study are listed below.

Objectives	**Outcome Measures**
Primary Objective To investigate whether, in patients with heart failure, an integrated data exchange, data analysis and risk prediction service capable of providing real-time alerts and advice to patients and predictive clinical decision support tools to healthcare practitioners leads to a **greater increase in the use of recommended medical therapy** than home monitoring with the same monitoring equipment but without the use of the integrated and personalized data analysis and decision support system.	Optimal medical therapy is defined as treatment consistent with the NICE guidelines for management of patients with chronic heart failure and will be measured as a composite opportunity score.
Secondary Objectives To investigate whether participants in the intervention arm achieve **higher levels of physical well---being** than those in the control arm To investigate whether participants in the intervention arm achieve **lower levels of risk of adverse outcomes** than those in the control arm	Physical functioning domain of the Minnesota Living with Heart Failure questionnaire and changes to self-assessed NYHA class Changes to the validated MAGGIC risk score and blood BNP / NT-pro-BNP
Tertiary Objectives To investigate the safety of IT-supported drug management To estimate adherence with home monitoring system	Composite of cardiovascular death, cardiovascular admissions (including renal failure and hypotensive episodes), unscheduled outpatient visit The proportion of participants' who discontinue monitoring before the end of study Recruitment rate, intervention and service

To estimate resource utilization	utilization costs

7 TRIAL DESIGN

SUPPORT-HF 2 will be a multicentre two-armed partially blinded parallel randomised controlled trial with a run-in period of up to 2 weeks between screening and baseline assessment. Three planned study visits will take place at participants' homes. Other interactions will be done remotely with the use of the study IT system or by telephone. Over-the-air downloads will occur from time to time to update the personalized software application on the participant's tablet computer. An overview of the trial design is provided in APPENDIX A: TRIAL FLOW CHART.

8 PARTICIPANT SELECTION CRITERIA

8.1 Trial Participants

Adults with confirmed diagnosis of heart failure (irrespective of the underlying aetiology) with the potential to benefit from home monitoring and management will be potentially eligible for recruitment into the study.

8.2 Inclusion Criteria

- Participant is willing and able to give informed consent for participation in the trial.
- Male or female, aged 18 years or above.
- Diagnosed with heart failure, defined as presence of typical symptoms (e.g. breathlessness, ankle swelling, and fatigue) and signs (e.g. elevated jugular venous pressure, pulmonary crackles, and displaced apex beat) resulting from an abnormality of cardiac structure or function.
- Potential to benefit from home monitoring and management defined as:
    - Self-assessed NYHA class II to IV; or
    - **BNP >100 pg/L or NT-pro-BNP >360 pg/L (according to the local laboratory methods used) in the last 30 days**

    AND either
    - Not on optimal therapy (in view of the Investigator), or
    - Probability of death within one year >10% (MAGGIC integer score 20 or more), or
    - At least one hospital admission related to heart failure in the previous 12 months.

8.3 Exclusion Criteria

The participant may not enter the trial if ANY of the following apply:

- No reliable 3G mobile or WiFi network connectivity at home
- Unable to read or speak English
- Any other significant disease, including critical unstable or end-stage heart failure, which, in the opinion of the Investigator, may either put the participant at risk because of participation in the trial, or may influence the result of the trial, or the participant's ability to participate in the trial.

9 TRIAL PROCEDURES

A summary of the practical procedures in presented in APPENDIX B: SCHEDULE OF PROCEDURES.

9.1 Recruitment

The study will be conducted at 4 UK sites (with the possibility of extending the number of participatings sites to maintain recruitment rates). Study sites will be hospitals and their affiliated primary care and community services that are involved in management of patients with heart failure. Integration of the study home monitoring data with the participants' electronic health records (EHR) is a requirement for site approval. Sites are expected to screen about 20 potentially eligible partipants per week.

Potentially eligible participants will be identified from hospital wards prior to discharge, cardiology outpatient clinics, and community heart failure nurse clinics, or by reviewing the hospital discharge lists and referral lists to community heart failure nurses. Potentially suitable patients will be asked for their permission to be approached by the study team. Additionally, patients can self-nominate for participation by contacting the research team directly.

When potential participants have been identified on the wards and clinics, an authorized member of research team will approach them once they are clinically stable and seeks their permission to speak to them about the trial. Participants who express an interest in the study will be given a *study information flyer* with a brief introduction to the study purpose and procedures, including a demonstration of the study self-monitoring equipment (computer tablet and Bluetooth sensors/monitors). Those who continue to express an interest in the study will receive a *participant information letter* and will be advised to inform the SUPPORT-HF team if they are interested in taking part in the study or offer them the option of making provisional arrangements for a screening visit after their discharge.

Those identified from hospital discharge lists and referral lists will be sent an *invitation letter* in the name of the Local lnvestigator (a member of patient's healthcare team). The letter will be accompanied by the study information flyer. Patients will be asked to contact the research team if they are interested in participating. Non-responders may be sent a second invitation letter. Those who contact the research team will be given the opportunity to ask questions, and find out more about the study. Those who continue to express an interest in the study will receive a participant information letter and a home screening visit will be arranged.

A log-file of all patients approached directly or indirectly will be kept by the Local Investigator (or a deputy) for screening purposes.

The study will also offer the opportunity to participants to self-nominate for inclusion in the trial, provided they are associated with one of the approved study sites.

9.2 Informed Consent

The participant must personally sign and date the latest approved version of the Informed Consent form before any trial specific procedures are performed.

Written and verbal versions of the Participant Information Letter and Informed Consent will be presented to the participants detailing no less than: the exact nature of the trial; what it will involve for the participant; the implications and constraints of the protocol; the potential risks and benefits involved

in taking part. It will be clearly stated that the participant is free to withdraw from the trial at any time for any reason without prejudice to future care, and with no obligation to give the reason for withdrawal.

The participant will be allowed as much time as wished to consider the information, and the opportunity to question the Investigator, their GP or other independent parties to decide whether they will participate in the trial. Written Informed Consent will then be obtained by means of participant dated signature and dated signature of the person who presented and obtained the Informed Consent. The person who obtained the consent must be suitably qualified and experienced, and have been authorised to do so by the Principal Investigator. A copy of the signed Informed Consent will be given to the participant. The original signed form will be retained at the trial site.

9.3 Screening and Eligibility Assessment

The screening visit will take place in participant's home. Home visits will be conducted with reference to guidance provided in our SOP Safety of Research Staff in the Community. At the screening visit, a member of the research team will demonstrate the study home monitoring system (again), check inclusion and exclusion criteria, record relevant current medication, and details of medical and heart failure history. Participants who appear to be eligible will have the study explained to them by the research staff. This will include going over the participant information letter together and a demonstration of the remote monitoring system. Consenting participants will enter the study run-in phase, which will last up to 2 weeks. During this time, participants and their caregivers will be asked to use the SUPPORT-HF home monitoring system. Their GPs and heart failure nurses and cardiologists (as applicable) will be informed about their enrolment into the study and its potential implications for further management, which will include intermittent blood tests and possible specialist recommendations for changes to their medication. At the screening home visit a blood test will be taken to check blood electrolytes, renal function and brain-natriuretic peptide (BNP) level. The blood sample will be sent to the local laboratory for analyses and later review. Additionally, a recent echocardiogram report will be obtained. With participant's permissions, some photos or video clips of the participant using the system may also be taken.

9.4 Randomisation, Blinding and Risk of Bias

The baseline visit will take place in participant's home. At the baseline visit a final eligibility check will be carried out. Participants will also be asked if they have experienced any SAEs since their previous visit.

Participants who are ineligible will return the SUPPORT-HF equipment to the study staff and the reason for ineligibility will be explained to them. The reason will be recorded for future tabulation.

Willing and eligible participants will be randomised to the study intervention or control arm by the central research staff within a working day after the home visit using a web-based randomisation programme. The randomisation procedure, based on a minimization algorithm, will stratify for type of heart failure (systolic vs. other), their baseline risk of death (within a pre-specified range of MAGGIC score) and study site. The randomisation schedule will be developed and kept by George Clinical, the independent Academic Research Organisation (ARO) responsible for trial management.

In a trial of home monitoring and management, it is impossible to fully blind participants and study staff to study treatment and this can bias effect estimates towards the intervention. To reduce the potential for such biases, both treatment groups will retain and use the SUPPORT-HF monitoring system. The

control group will be conceptualized as an attention control, rather than a usual-care control, to minimize problems such as a placebo effect, and a "loser" effect that could systematically change the behaviour of participants. In addition, the participants will be blinded from the actual study hypothesis by providing positive names for the trial groups (i.e., "enhanced self-management" for the control group and "supported medical management" for the intervention group). Participants in both groups will be informed that the SUPPORT-HF system is not a replacement for their usual clinical care, and that in the event of deterioration in their health they should contact their own doctor or nurse as usual. In addition, the trial will restrict access to the information on treatment allocation as much as possible. Whilst the central clinical and technical management team must know each individual participant's treatment allocation for adaptation of the software application on the tablet (providing increased level of personalisation during the trial, using over-the-air downloads) and provision of the intervention, all other members of the team, in particular those collecting subjective study outcome information, will not be made aware of treatment allocation. Furthermore, we will separate the statistical evaluation into two parts. Members of the formative evaluation team will have access to treatment allocation and will use all data collected for iterative adaption of the monitoring and management system. The summative evaluation team, however, will conduct all randomised comparisons without being aware of treatment allocation.

This proposed method is one of the most rigorous approaches possible in such open-label trials to achieve an unbiased estimate of treatment effects. However, the introduction of an active control group may dilute treatment effects. Nonetheless, as the discussion document in APPENDIX C: IMPLICATIONS OF ACTIVE VS USUAL CARE CONTROL summarises, on balance, the advantages of this approach appear to outweigh its disadvantages in SUPPORT-HF 2.

9.5 Study Procedures during Follow---up Period

In addition to the diary questionnaire, participants in both arms will be prompted by the tablet computer to respond to questions relating to their health, medication use, doctor visits, and hospitalisations during follow-up (see APPENDIX B: SCHEDULE OF PROCEDURES). For those reporting SAEs and for those who have not used the system for some time, complementary telephone assessments for collection further information on possible study outcomes will take place.

In SUPPORT-HF 1, the median time taken for daily monitoring activities was less than 2 minutes. In addition to these active monitoring procedures, the SUPPORT-HF tablet will passively collect information on timing and usage of the SUPPORT-HF software application. Some patients will also be asked to use passive physical activity monitoring equipment such as the FitBit (a bracelet that can record levels of physical activity during the day and monitor sleep quality at night) for specific periods of time. Participants will be provided with contact details of the study staff for any questions and comments that they may have in relation to the use of the equipment. In addition, the tablet computer allows patients and their caregivers to send a contact request to the team by pressing a button. The central study team will also contact patients if no recordings have been transmitted for more than 10 days.

9.6 Subsequent Visits

After the baseline visit, there will be no routine home visits until the final visit, when the SUPPORT-HF study system will be collected and a final assessment will take place (see APPENDIX B: SCHEDULE OF PROCEDURES).

9.7 Discontinuation/Withdrawal of Participants from Trial Treatment

All participants have the right to withdraw from the trial at any point, without providing a reason. Those participants who do withdraw from the trial will be asked if they would be willing to provide follow-up information through telephone calls or record linkage during the trial period. If the participants decline, no further information will be collected.

In addition, the Investigator can withdraw participants from the trial, e.g. when continued participation is not in the participant's interest due to disease progression or inability to comply with study treatment. Withdrawal from the trial will not result in exclusion of the data for that participant from analysis (to reduce the risk of bias from loss-to-follow-up in an intention-to-treat design). The reason for withdrawal will be recorded in the CRF. If the participant is withdrawn due to an adverse event, the Investigator will arrange for follow-up visits or telephone calls until the adverse event has resolved or stabilised.

9.8 Definition of End of Trial

The end of trial is the date of the last home monitoring recording received from the last participant.

10 INTERVENTION DESCRIPTION

10.1 SUPPORT---HF Platform

The SUPPORT-HF system integrates a touch-screen tablet computer, used as a front-end and communication gateway for participants, and various sensing devices including a blood pressure and heart rate monitor and a weighing scale (see Figure 1).

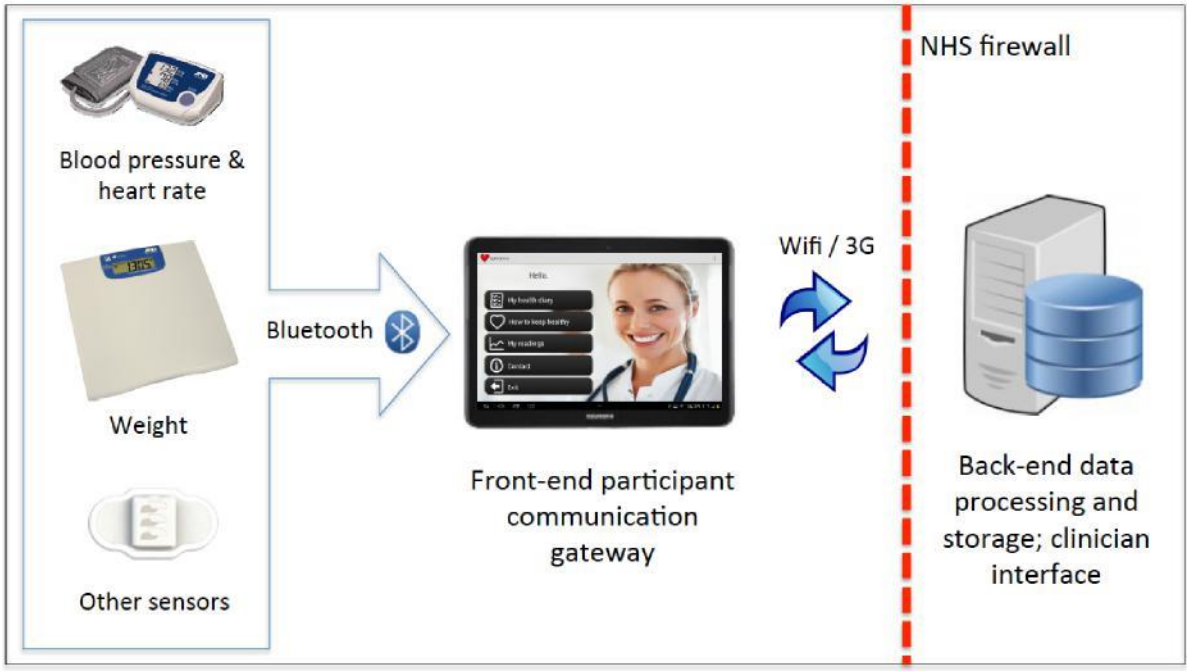


Figure 1: SUPPORT-HF 2 data acquisition and exchange platform

Bluetooth is used for delivering monitoring data from the sensors to the tablet computer, which in turn transfers the data through the internet to a back-end infrastructure located on secure NHS servers for storage, processing, and display to the clinical research team and patient's direct care team. This

platform will be the same for both study groups. However, the degree of personalisation, the processing of the information and the feedback to participants and healthcare professionals will differ substantially between the two groups.

10.2 Enhanced Self-Management

Figure 2 provides an overview of the system architecture in the Enhanced Self-Management group.

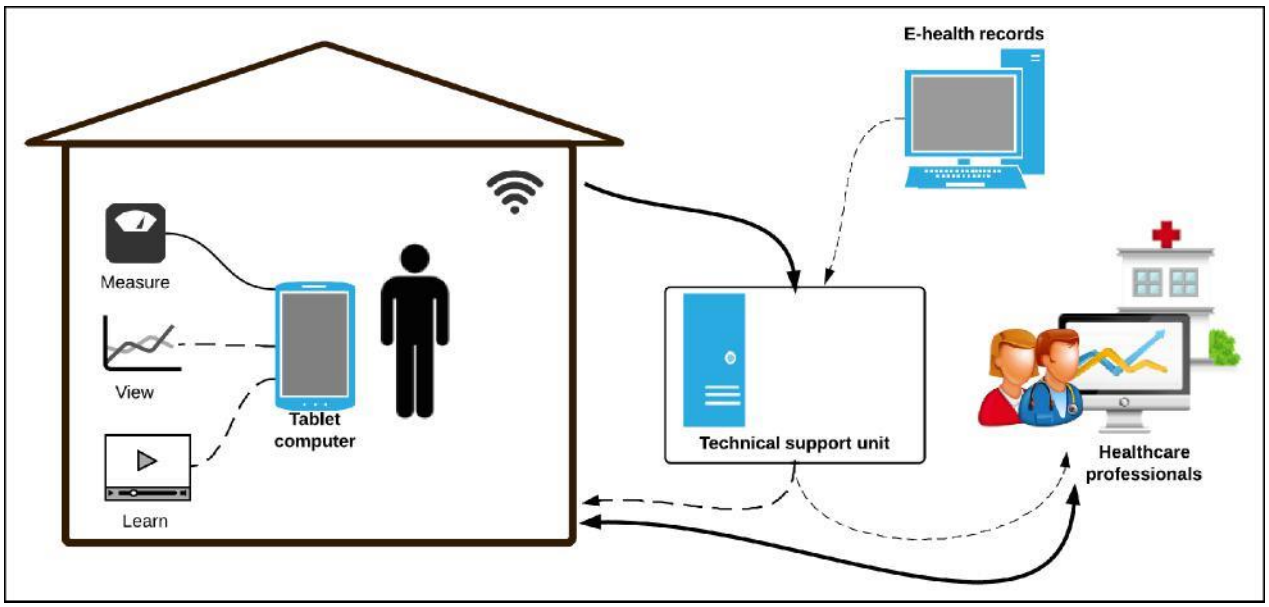


Figure 2: System features of the Enhanced Self-Management group

Measurement: Participants allocated "Enhanced Self-management" will be asked to monitor their health by taking daily measurements of their weight, blood pressure and pulse, and by completing a brief symptom questionnaire. Health-related quality of life (EQ5-D and Minnesota Living With Heart Failure) will be assessed at screening visit and then at 2-monthly intervals.

Integration with clinical pathways: The home monitoring data will be linked to participants' EHR for retrieval of additional outcome measures but such information will not be accessible to the study team during the course of the study and will be used for final trial evaluation only. Data collected by participants will be accessible to their healthcare professionals in its raw format with no ranking or interpretation.

Feedback and self-management support: Participants are able to view their previous readings, displayed in a graphical format, and use the self-management module of the tablet computer, which contains generic educational material such as animations and video clips on heart failure and strategies for managing it. Home monitoring measures that are considered to be clearly abnormal as per current practice guidelines (i.e., an increase in weight by 2-3 kg over 2-3 days) will be flagged and participants will receive immediate automated feedback via the tablet computer to contact their doctor or nurse for further advice. If no such flags are raised, participants will receive a message at the end of their session to indicate that their readings are within an acceptable range. Participants will also be able to contact the technical and administrative team for any study-related questions that they may have by simply pressing a button on the tablet computer. This will trigger email and text messages to authorised research staff who will usually get back to the participant within two working days.

Participants will be reminded that this system does not replace their usual care and if they have any health-related questions they may wish to contact their own doctor or nurse.

10.3 Supported Medical Management

Figure 3 provides an overview of the system architecture in the Supported Medical Management group.

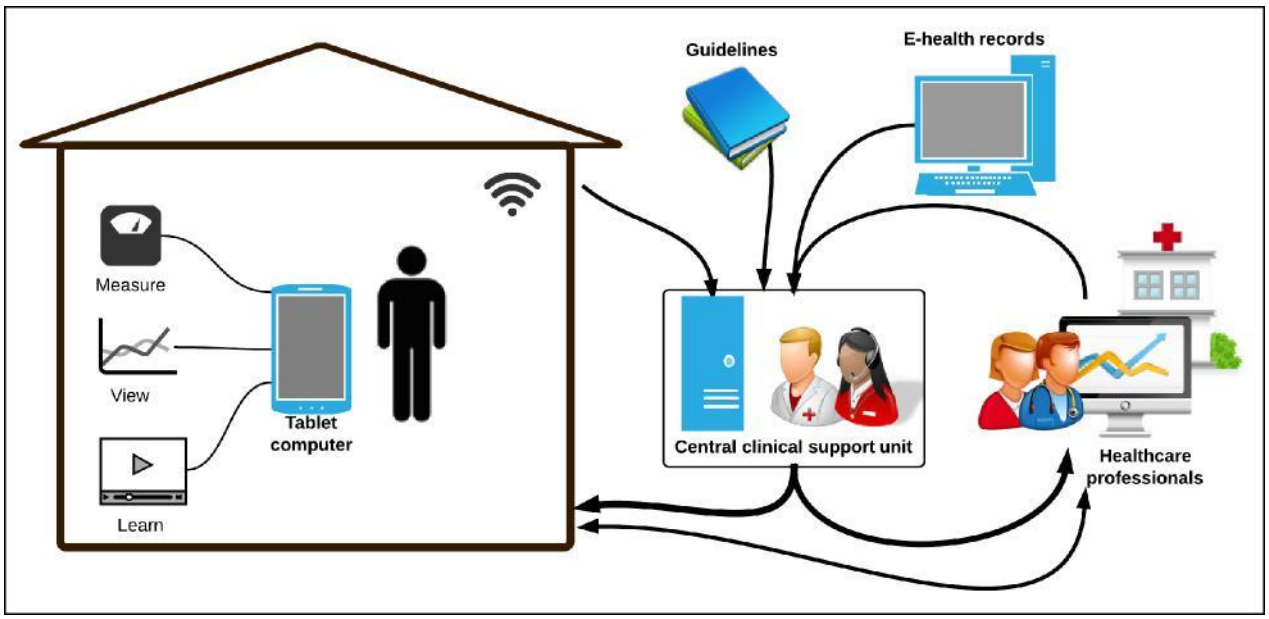


Figure 3: System features of the Supported Medical Management group

Measurement: Participants allocated "Supported Medical Management" group will be provided with exactly the same equipment and will start with exactly the same monitoring scheme.

Integration with clinical pathways: The core of the intervention is an integrated central clinical support unit consisting of a cardiologist, a heart failure nurse, engineers and administrative support personnel. The support unit will have full access to the home monitoring data, which will be linked to participants' EHR for retrieval of the current medication plan and test results. It will iteratively adapt and use a statistical machine learning engine that integrates all data collected from the home monitoring equipment (including those from the SUPPORT-HF 1 study) as well as the EHR and clinical practice guidelines to generate a continuously updated risk prediction and clinical decision support tool.

Feedback and self---management support: The support unit will use the baseline information from each participant to 'personalise' the educational material and to devise a personal treatment strategy. Based on participant's health status and type of heart failure certain types of educational material will be activated or deactivated. Previous readings will be displayed as simple colour-coded graphs on the participant's tablet computer to facilitate better understanding of which measures are abnormal and which are acceptable. A detailed SOP will specify the clinical management algorithms for participants in the intervention group and how the central clinical support unit will take actions during the course of the study. In brief, patients will be ranked according to their need for monitoring and change in their management plan. Those who are symptomatic or clinically unstable will be flagged for more intensive reviewing of their measures and adaptation of their medication. Those that are stable but not on optimal therapy yet will be flagged for medication up-titration to target doses under monitoring of haemodynamic status and renal function according to clinical guidelines. Any suggested changes to

medications or the need for blood tests for safety and efficacy monitoring will be communicated to participants as well as their healthcare professionals. Depending on the participant's usage record, personalised messages will be sent electronically to motivate them for engagement with self-management activities, according to their need and capacity.

We expect that by distilling data into actionable information this computer-guided alert setting and management system will lead to completion of recurrent and time-consuming tasks much more reliably and with less need for face-to-face specialist input compared to the prevailing models of care delivery.

Participants will be reminded that this system does not replace their usual care and if they have any health-related questions they may wish to contact their own doctor or nurse.

11 SAFETY AND OUTCOME REPORTING

11.1 Definitions

A serious adverse event (SAE) is any untoward medical occurrence that:

- results in death
- is life-threatening
- requires inpatient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity

Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences.

11.2 Procedures for Recording Serious Adverse Events and Other Study Outcomes

All SAEs occurring during the trial that are observed by the Investigator or reported by the participant, their caregivers or healthcare professional will be recorded on the CRF as soon as these are brought to the attention of the Investigator.

The following information will be recorded: description, date of onset and end date. Non-serious AEs will not be recorded routinely, unless such events are thought to be related to the study treatment by participants or the Investigator or unless they are trial outcome measures.

Other trial outcomes (health monitoring data and quality of life and utility score) will be directly reported by the participants with the use of the home monitoring equipment or through the planned 3-monthly telephone calls. Information on healthcare utilization and medical investigations will be captured directly through EHR.

12 STATISTICAL ANALYSIS

We will distinguish two types of statistical analyses in this study. The first one will be a formative evaluation of study processes and the second one will be a summative analysis of the trial outcomes. The statistical teams working on the formative evaluation will be distinct from the summative statistical team. This is to allow continuous adaptation of the intervention components and contents without compromising on the rigour of randomised comparisons.

More detailed Statistical Analysis Plans will be developed. A brief overview of these is outlined here.

12.1 Formative Evaluation

The formative statistics are aimed at continuous improvement of the home monitoring and management system during the course of the trial in order to ensure maximum fidelity of the intervention functions, in both trial arms. To achieve this, the analytics team will have access to all recorded information (as in SUPPORT-HF 1) and will use this to refine the system features, the user interface design, as well as the type and order of questions being asked. In the intervention arm the analytics team will further work closely with the clinical team to improve the risk prediction and clinical decision algorithms over time. The risk models will range from basic machine learning algorithms (including standard regression, classification and clustering/segmentation models), to more advanced multivariate hierarchical models and Bayesian models that take into account the prior information (from medical literature, clinical experts, etc.) as well as EHR data. Such an approach is expected to score patients for various risks, which can then be used for actionable recommendations such as urgent visit and/or hospitalisation. The formative assessment group will not be involved in the acquisition of trial outcomes or in the final blinded statistical analyses.

12.2 Summative Statistical Methods

The purpose of the summative statistical analyses is to rigorously test the trial hypotheses. A detailed analysis plan will be developed prior to access to the trial results. Once collection and verification of clinical outcomes has been completed, the pre-specified statistical analyses will be conducted. All analyses will be conducted according to 'intention-to-treat'.

12.3 Method for Primary Outcome Measurement

The primary outcome of the trial is "optimal medical therapy" defined as treatment consistent with NICE guidelines for management of patients with chronic heart failure. Optimal medical therapy will be measured as an opportunity score across all participants in each treatment arm. The opportunity score will be the total number of times a treatment was given, divided by the total number of chances that providers had to give the treatment to the participants,[16] calculated for each treatment arm separately. Because the management of patients with systolic dysfunction differs substantially from those without systolic dysfunction, the opportunity scores for these participants will be calculated separately first and then aggregated with a weighting factor that represents the fraction of participants with or without systolic dysfunction. Thus, the opportunity score (OS) is:

$$OS_i = w_s \frac{si}{s1} + w_d \frac{di}{di}$$

$$OS_c = w_s \frac{sc}{sc} + w_d \frac{dc}{dc}$$

With

i being the intervention arm, and c the control arm

w being the weighting factor

s being patients with systolic dysfunction and d patients with no systolic dysfunction

T being the sum of total indicators that all patients were eligible for at the beginning of the study

t being the sum of indicators that patients received at the end of the study (or at the last follow-up if patients died or were lost to follow-up)

The number of indicators that patients are eligible for will be based on the NICE guidelines for management of chronic heart failure[11] and additional NICE technology appraisals for specific interventions such as ivabradine.[17] This will take account of type of heart failure (systolic vs other), self-reported symptoms at the beginning of study (average of NHYA class during run-in period), and in those with preserved systolic function, the underlying diseases that would require medical management (mainly atrial fibrillation and blood pressure). At the final evaluation, the current management plan and the self-reported NYHA class will be used to calculate the sum of treatment targets achieved for each patient. This method will not take account of the appropriateness of treatment at the end of study. However, in a randomised comparison, we expect that any reasons against usage of medical therapy that may arise during the course of the study to be balanced between groups, and hence, not a source of bias.

12.4 Sample Size Estimation

Given that many patients with optimal medical therapy will be excluded from participation into the trial and in face of existing gaps in the system for optimisation of drug therapy in the community, we assume the opportunity score in the control group to be 0.5 (i.e., at the end of the study, participants will have received 50% of the treatment recommendation that they would have been eligible for as assessed at the beginning of the study). In the absence of any previous similar studies, the effect of the intervention is difficult to predict but we assume that an absolute net difference in the use of appropriate medication by 25% between the intervention and control arms to be clinically worthwhile and realistic. With these assumptions, randomisation of 85 participants per trial arm will provide 90% power ($2\alpha=0.05$) to detect an absolute 25% difference in the primary outcome between the trial arms. To take account of attrition, we estimate that a total 200 participants will be needed for comparisons.

Assuming the mean score in physical subscale of the MLWHF questionnaire to be 25 (SD 10) in the control group,[18] randomisation of 200 patients will also have 90% power at two-sided alpha 0.5 to detect a 5 point difference in MLWHF physical subscale between the two groups at the end of the study, or 75% to detect a 4 point difference in the subscale.

13 DATA MANAGEMENT

13.1 Source Data

Source documents are where data are first recorded, and from which participants' case record form (CRF) data are obtained. These include, but are not limited to, hospital records (from which medical history, previous and concurrent medication, laboratory data and hospitalisation episodes may be summarised into the CRF), home monitoring diaries, and correspondence with study staff.

CRF entries will be considered source data if the CRF is the site of the original recording (e.g. there is no other written or electronic record of data). All documents will be stored safely in confidential conditions. On all trial-specific documents, other than the signed consent and data stored behind the NHS firewalls, the participant will be referred to by the trial participant number/code, not by name.

13.2 Access to Data

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

13.3 Data Recording and Record Keeping

A schematic overview of the trial data management system is provided in Figure 4.

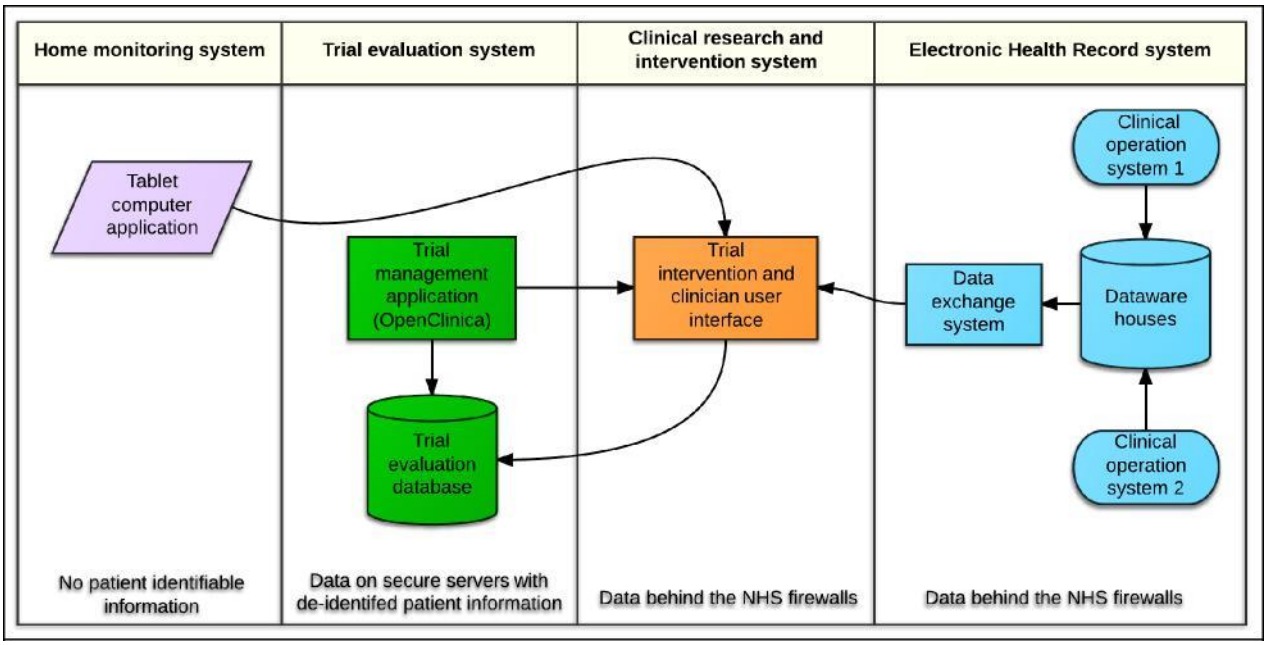


Figure 4: Trial data management system

The SUPPORT-HF data management system is designed in such way that standard clinical operational databases that support care delivery are not used directly to support research and analysis. Instead, a separate dedicated research and intervention system is developed (behind the NHS firewalls) to allow testing of the data-driven clinical management system in a secure and integrated way. Then, a second system is being used for evaluation of the trial, containing only information that is necessary for addressing the research in questions, and adequately insulated from the "live" care systems.

The SUPPORT-HF 2 study IT system will consist of custom-written applications as well as commercially available applications. Tablet computers will have a custom-written (android or iOS) application for data acquisition from sensors or monitors and for data exchange with a secure server behind the NHS firewall. Tablet computers will not store any patient identifiable information. All data on the tablet computers will be securely transmitted wirelessly to the SUPPORT-HF back-end clinical intervention system (in the form of a web-based application). The back-end system will be used by the clinical team for disease management according to allocated user rights. The back-end system will be secured by the NHS firewall and will allow access to patient identifiable information only to authorised clinical users. The back-end system will send data periodically to the OpenClinica database for storage and analysis and will intermittently extract data from other EHR databases (e.g., via a communication interface) in an automatic manner. Such data will include laboratory results, PACS or other imaging information, hospital admission episodes or clinic visits, and medication prescriptions.

The back-end system and the tablet computer software application will be used for participants' management of clinical information. SUPPORT-HF 2 research staff will use OpenClinica as a web-based tool for the trial's electronic data management, i.e., direct participant data entry (e.g., completion of eCRF and SAE reporting) as well as centre management and central statistical monitoring. OpenClinica will also automatically exchange information with the back-end system. OpenClinica database will hold only de-identified data from study participants. A separate database will maintain an association between study identifiers, NHS numbers, and any other identifiers used in the EHR. This database will be used to exchange data automatically between OpenClinica and the back-end system. The de-identified data collected on OpenClinica will be stored on secure study servers and form the basis for summative trial analysis.

All accesses to OpenClinica will be managed by George Clinical and will require a unique username and password. Any changes to data will require the users to enter their credentials as an electronic signature. Staff access will be restricted according to their role within the study.

14 QUALITY ASSURANCE PROCEDURES

The trial will be conducted in accordance with the current approved protocol, relevant regulations and standard operating procedures. George Clinical will independently monitor data quality and study sites.

15 ETHICAL AND REGULATORY CONSIDERATIONS

15.1 Declaration of Helsinki

The Investigator will ensure that this trial is conducted in accordance with the principles of the Declaration of Helsinki.

15.1 Guidelines for Good Clinical Practice

The Investigator will ensure that this study is conducted in accordance with relevant regulations and with Good Clinical Practice.

15.2 Approvals

The protocol, informed consent form, participant information letter and any proposed advertising material will be submitted to an appropriate Research Ethics Committee (REC) and host institution(s) for written approval.

The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

15.3 Participant Confidentiality

The trial staff will ensure that the participants' anonymity is maintained. The participants will be identified only by initials and a participant's ID number on the CRF and any electronic database. All documents will be stored securely and only accessible by trial staff and authorised personnel. No patient-

identifiable information will be stored on the tablet PCs. The trial will comply with the Data Protection Act, which requires data to be anonymized as soon as it is practical to do so.

15.4 Expenses and Benefits

Reasonable travel expenses for any visits additional to normal care will be reimbursed on production of receipts, or a mileage allowance provided as appropriate.

15.5 Other Ethical Considerations

We do not foresee any ethical concerns or risks to the patients' health or wellbeing since none of our evaluation methods entail intrusive procedures.

16 FINANCE AND INSURANCE

16.1 Funding

The trial is funded by a NIHR Career Development Grant to the CI and is further supported by the NIHR Oxford BRC, the George Institute for Global Health and the Oxford Martin School.

16.2 Insurance

The University has a specialist insurance policy in place which would operate in the event of any participant suffering harm as a result of their involvement in the research (Newline Underwriting Management Ltd, at Lloyd's of London). NHS indemnity operates in respect of the clinical treatment which is provided.

17 PUBLICATION POLICY

The SUPPORT-HF 2 Steering Committee members, Investigators and Collaborators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study. Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged. We will also aim to publish this work with an open access journal to ensure that it is widely available. Authors will acknowledge that role of the funders in any publication arising from the study. All publications and release of data will be compliant with relevant regulations and recommendations on transparency in clinical research.

18 REFERENCES

1. National Heart Failure Audit: April 2011 - March 2012. 2013;

2. Kalra PR, Morley C, Barnes S, et al. Discontinuation of beta-blockers in cardiovascular disease: UK primary care cohort study. Int J Cardiol 2012;:5–9.

3. Hancock HC, Close H, Fuat A, Murphy JJ, Hungin APS, Mason JM. Barriers to accurate diagnosis and effective management of heart failure have not changed in the past 10 years: a qualitative study and national survey. BMJ Open 2014;4(3):e003866.

4. Christensen CM, Grossman JH, Hwang J. The Innovator's Perscription: A disruptive solution for health care. New York: McGraw Hill; 2009.

5. Anker SD, Koehler F, Abraham WT. Telemedicine and remote management of patients with heart failure. Lancet 2011;378(9792):731–9.

6. Desai AS, Stevenson LW. Connecting the Circle from Home to Heart---Failure Disease Management. N Engl J Med 2011;363(24):2364–7.

7. Pandor A, Thokala P, Gomersall T, et al. Home telemonitoring or structured telephone support programmes after recent discharge in patients with heart failure: systematic review and economic evaluation. Health Technol Assess 2013;17(32):1–207, v–vi.

8. Koehler F, Winkler S, Schieber M, et al. Impact of Remote Telemedical Management on Mortality and Hospitalizations in Ambulatory Patients With Chronic Heart Failure / Clinical Perspective. Circulation 2011;123(17):1873–80.

9. Steventon a., Bardsley M, Billings J, et al. Effect of telehealth on use of secondary care and mortality: findings from the Whole System Demonstrator cluster randomised trial. Bmj 2012;344(jun21 3):e3874–e3874.

10. McMurray JJ, Adamopoulos S, Anker SD, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart. Eur Hear J 2012;33(14):1787–847.

11. NICE. CG108 Chronic heart failure: full guideline.

12. Rahimi K, Patel A, Macmahon S. Two decades of research on innovative models of care delivery for patients with heart failure: the end or just the beginning? Arch Iran Med 2012;15(7):439–45.

13. Chaudhry SI, Mattera JA, Curtis JP, et al. Telemonitoring in Patients with Heart Failure. N Engl J Med 2010;363(24):2301–9.

14. Desai AS, Stevenson LW. Rehospitalization for heart failure: predict or prevent? Circulation 2012;126(4):501–6.

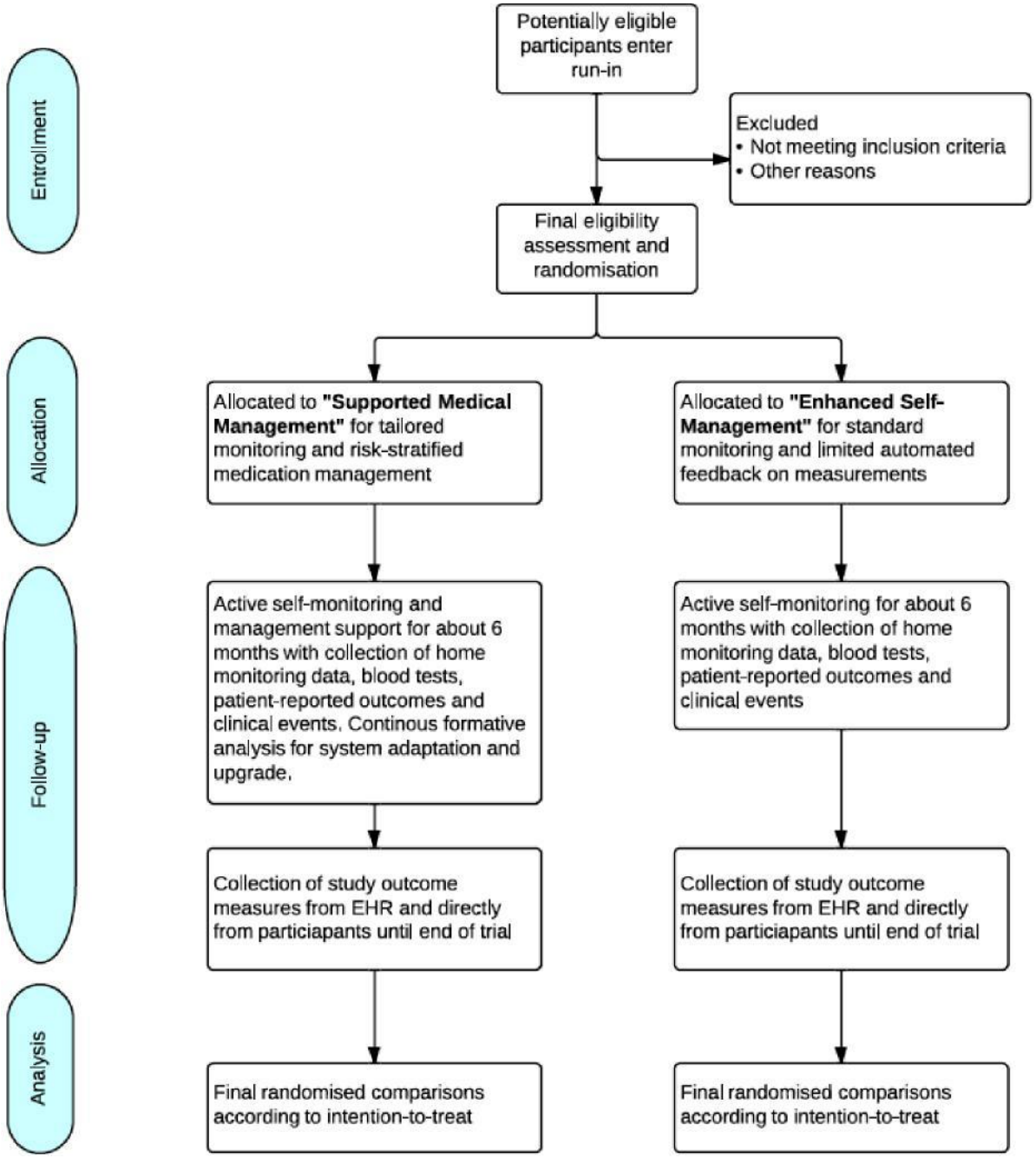
15. Kohler F, Winkler S, Schieber M, et al. Telemedical interventional monitoring in heart failure (TIM---HF), a randomized, controlled intervention trial investigating the impact of telemedicine on mortality in ambulatory patients with chronic heart failure. Circulation 2010;122:2224 (abstract 21835).

16. Peterson ED, DeLong ER, Masoudi F a, et al. ACCF/AHA 2010 Position Statement on Composite Measures for Healthcare Performance Assessment: a report of American College of Cardiology Foundation/American Heart Association Task Force on Performance Measures (Writing Committee to Develop a Position Stat. J Am Coll Cardiol 2010;55(16):1755–66.

17. NICE. Chronic heart failure --- ivabradine.

18. Hoekstra T, Jaarsma T, van Veldhuisen DJ, Hillege HL, Sanderman R, Lesman---Leegte I. Quality of life and survival in patients with heart failure. Eur J Heart Fail 2013;15(1):94– 102.

19 APPENDIX A: TRIAL FLOW CHART



20 APPENDIX B: SCHEDULE OF PROCEDURES

Procedures	Visits		Telephone calls during follow-up	Final visit
	Screening	Baseline	Minimum 3-monthly	
Informed consent	x			
Demographics	x			
Medical history	x			
Current medications	x	x		
Biochemistry, renal function and BNP Test,	x		(x)*	x
Echocardiogram Report	x			
Eligibility assessment	x	x		
Randomization		x		
Usability questionnaire		x		x
Adverse event assessments		x	x	x

* The frequency of blood investigations will differ by treatment allocation and it is envisaged that most requests during follow-up will be made to participants' own doctors or nurses.

21 APPENDIX C: IMPLICATIONS OF ACTIVE VS USUAL CARE CONTROL

Favours active control	Reasons for an active control arm		Reasons against active control arm	Favours usual care
	Design considerations			
	Enables the introduction of an active run-in phase for better selection of patients who are more likely to benefit from the intervention and to continue to stay in the study			
	Ethical considerations			
	Easier to seek informed consent, given that all patients will receive the devices		Patients in control arm may erroneously assume that they are under active follow-up	
	Devices won't be taken away from patients after run-in			
	Costs and resource implications			
	Faster recruitment due to simplification of consenting and greater acceptability to participants. This makes trial conduct more efficient.		Doubling in device cost (about £300 more per each randomised patient)	
	Automated processes for requests for ordering bloods to increase efficiency		Additional running costs for device maintenance, technical support, possibly blood tests	
	Automated processes for event follow-up to increase efficiency		Additional running cost of development of two software systems	
	Scientific considerations			
	Attention control, which diminishes the risk of 'false-positive' study findings as a result of greater attention given to study participants in the active arm (even without the remote monitoring intervention)		Potential for treatment effect dilution, in particular for subjective outcomes, such as quality of life	
	Unbiased standardised collection of self-reported outcomes			
	Unbiased standardised data for behavioural data (e.g. usage of the system)			
	Use of self-monitoring data in the control arm for risk prediction			
	Impacts of the study findings			
	Clear communication that its not the equipment but the software and processes		Some patients in the control arm may become dissatisfied with the support that they are receiving during the course of the study	
	Study findings make the study scientifically more rigorous		Active control makes the findings less policy-relevant (but can be addressed in subsequent modelling tests)	
	Overall decision			

22 APPENDIX F: AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
	0.1	30/04/2014	KRahimi	First draft
	0.2	12/05/2014	KRahimi	Revision, incorporating comments from investigators and collaborators
	0.3	07/06/2014	KRahimi	After CTRG review
	0.4	20/06/2014	KRahimi	After second CTRG review
	1.0	01/07/2014	KRahimi	After third CTRC review
Minor – 1	2.0	07/05/2015	KRahimi	Added Echocardiogram to Schedule of Procedures

Protocol amendments must be submitted to the Sponsor for approval prior to submission to the REC committee.