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)

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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 SYNOPSIS

Trial title	Home monitoring with integrated risk-stratified disease management support versus home monitoring alone in patients with heart failure: 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 to monitor and manage their own health - in particular when supported by healthcare professionals remotely - may improve patient outcomes and reduce healthcare utilisation. However, robust evidence for clinical effectiveness and cost-effectiveness of such an IT-supported disease management system is lacking.	
Hypothesis	In patients with heart failure, home monitoring with an integrated data analysis and risk prediction service, which provides tailored alerts and advice to patients and predictive clinical decision-support tools to healthcare practitioners (GPs, nurses and hospital cardiologists) 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 (with an expected invitation ratio of 2:3 for preserved to reduced ejection fraction patients) who have the potential to benefit from home monitoring and management.	
Planned sample size	350 (with plans to increase to over 1000 as a clinical endpoint study subject to successful interim reviews)	
Intervention	About 6 months (or until the end of trial)	
Follow-up duration	Active follow-up until the end of trial, passive follow-up through record linkage beyond the trial end date	
Planned trial period	October 2015 to May 2017	
Setting	10 to 15 sites across United Kingdom. Recruitment will be from hospitals, outpatient clinics, community or primary care. 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 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** when compared with home monitoring with the same monitoring equipment but without the use of the integrated and personalized data analysis and	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.

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	decision support system.	
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 **pilot all study procedures** and inform the decision about immediate progression of the trial into a substantive trial	Process outcomes to be measured include study site activation status, participant recruitment rate, observed event rates (death, hospitalisation), proportion of sites and patients with fully integrated system (EHR and home monitoring system), resource utilization (both trial and future service costs)
	To investigate **the bio-chemical and physiological efficacy** of IT-supported medicines management	Changes to the validated MAGGIC risk score[16] and blood BNP / NT-pro-BNP level at the end of trial for each participant; Proportion of patients in sinus rhythm who have a heart rate between 50-70bpm; proportion of patients with a serum potassium in the ideal range for HF (4.0-4.9mmol/L) at the end of trial for each participant
	To investigate the **clinical safety** of IT-supported medicines management	Composite of cardiovascular death, cardiovascular admissions (including renal failure and hypotensive episodes) and unscheduled outpatient visits by treatment allocation
	Supported Medical Management arm	**Enhanced Self-Management arm**
Intervention	**Planning**: Development of individualised management plan before randomisation (including major co-morbidities such as hypertension, atrial fibrillation) **Measurement**: 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 (EHR) for estimation of fluid status and risk. **Feedback and systematic**	**Planning**: Development of individualised management plan before randomisation (including major co-morbidities such as hypertension, atrial fibrillation) **Measurement**: 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 (EHR). **Feedback and systematic implementation:** Data collected will not be processed to provide personalised feedback to patients for self-

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	implementation: Protocol-based individualised monitoring and management supported by a specialist heart failure team and computer algorithms with individualised specialist treatment advice to patients and their doctors for drug and risk management.	management or to their doctors for risk-based monitoring and medicines management.
Expected outcome	This will be the first trial of a 'third-generation' remote monitoring system using commercially available, low cost devices enhanced by customised applications to predict risk and provide tailored management advice at scale. The finding of this will contribute to a planned large-scale trial with clinical effectiveness and cost-effectiveness as its primary outcomes (subject to funding review).	

3 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. While it is commonly expected that medical 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 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 as 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 or the necessary human resources for frequent monitoring that is needed for titrating medicines 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 and episodic 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

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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 long-term 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 must meet seven 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 numbers of patients than current systems can afford, (6) be clinically effective, and (7) be cost-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-centred, adaptive, integrated digital health platform. SUPPORT-HF 2 now aims to address the remaining five 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 possibly modest differences in healthcare outcomes and resource utilisation. The evaluation of the intervention must allow sufficient flexibility of the intervention to adapt iteratively to the changing environments (e.g., availability of newer technologies) without losing the value of randomised experiments which are ideally suited for detecting modest causal effects.[12] Furthermore, the context into which an intervention is to be introduced must be considered carefully. Integrated digital healthcare is likely to be most useful in contexts where quality of care is suboptimal 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. However, before embarking on a major clinical trial with clinical outcomes as its primary outcome, an internal pilot study will be conducted to ensure that all study procedures run smoothly and that extension of the pilot into a large-scale trial is feasible and worthwhile.

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4 OBJECTIVES AND OUTCOME MEASURES

The overall aim of the SUPPORT-HF 2 research programme is to develop and evaluate 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** when compared with 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	Physical functioning domain of the Minnesota Living with Heart Failure questionnaire and changes to self-assessed NYHA class
To **pilot all study procedures** and inform the decision about immediate progression of the trial into a substantive trial	Process outcomes to be measured include study site activation status, participant recruitment rate, observed event rates (death, hospitalisation), proportion of sites and patients with fully integrated system (EHR and home monitoring system), resource utilization (both trial and future service costs)
To investigate **the bio-chemical and physiological efficacy** of IT-supported medicines management	Changes to the validated MAGGIC risk score[16] and blood BNP / NT-pro-BNP level at the end of trial for each participant; Proportion of patients in sinus rhythm who have a heart rate between 50-70bpm; proportion of patients with a serum potassium in the ideal range for HF (4.0-4.9mmol/L) at the end of trial for each participant
To investigate the **clinical safety** of IT-supported medicines management	Composite of cardiovascular death, cardiovascular admissions (including renal failure and hypotensive episodes) and unscheduled outpatient visits by treatment allocation

5 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. Two planned study visits will take place at participants' homes or in clinic. Other interactions will be done remotely with the use of

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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.

6 SITE SELECTION AND ACTIVATION

The study will be conducted at about 10 UK sites (with the possibility of extending the number of participatings sites to maintain recruitment rates). Study sites will be hospitals, primary care or 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) (in particular lab results and clinical episodes (and if available medication, echocardiogramm and electrocardiogramm (ECG) reports) is a requirement for site approval. Site activation will prioritize sites who have an existing EHR integration platform that can be used for the purpose of the study. For sites who do not have a functionning EHR integration platform, a technical solution and implementation plan will be defined in collaboration with the site's IT department. This may involve the collaboration with a third party provider fulfilling the NHS security requirements, and may require the support from the site's IT resources.

Sites are expected to recruit about 5 to 10 participants per month with no preference for patients who have heart failure with preserved or reduced ejection fraction (expected invitation ratio of 2:3 for preserved to reduced ejection fraction patients). Sites' capactity to recruit sufficient number of patients will be assessed during a 2-week screening phase where Local Investigators (or their deputies) are asked to prospectively screen potentially eligble participants using the participant screening log.

7 PARTICIPANT SELECTION CRITERIA

7.1 Trial Participants

Adults with a 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.

7.2 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 (typically by a specialist), 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 (as evidenced by cardiac imaging and/or biomarkers such as BNP).
- Potential to benefit from home monitoring and management defined as:
    - Average self-assessed NYHA class II to IV in the week before randomisation; or
    - BNP >350 pg/mL (100 pmol/L) or NT-pro-BNP >1000 pg/mL (130 pmol/L) in the last 30 days, or
    - Not on optimal therapy as evidenced by the pre-randomisation personal management plan suggesting 2 or more treatment targets (see section Run-in Phase).
- High risk of adverse outcomes defined as:
    - Probability of death within one year >10% (MAGGIC integer score 20 or more[16]), or
    - At least one hospital admission related to heart failure in the previous 12 months.

7.3 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.

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8 TRIAL PROCEDURES

A summary of practical procedures is presented in APPENDIX A: SCHEDULE OF PROCEDURES in and a detailed project plan is uploaded with the application.

8.1 Study team

Due to the national set-up of the trial and the necessity for home visits, some of the study sites will establish local research teams to support the central SUPPORT-HF 2 study team in patient recruitment, visits and follow-up calls. The local research teams will consist of one or several community nurses (eg a research or a heart failure nurse). Prior to performing any trial-related activities, the local research team will follow a dedicated training on the SUPPORT-HF 2 trial procedures.

8.2 Recruitment

Potentially eligible participants will be identified from hospital wards prior to discharge, cardiology outpatient clinics, general practitioners, or community heart failure nurse clinics, or by reviewing the hospital discharge lists and referral lists to community heart failure nurses. Potentially eligible patients will be approached by the study team or the local care team. The study will also offer the opportunity to participants to self-nominate for inclusion in the trial, provided they are under clinical care at one of the approved study sites. A study website, www.supporthf.org, will present a brief overview of the study and relevant health information for patients and the general public, and will allow for interested readers to contact the study team for more information.

When potential participants have been identified on the wards and clinics and indicated their interest, a member of the research team or the local care team will approach them once they are clinically stable and seek 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 self-monitoring equipment (computer tablet and Bluetooth sensors/monitors). Those who express an interest in the study will receive a *participant information letter* and will be advised to inform the SUPPORT-HF 2 team if they are interested in taking part in the study or be offered 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 Investigator (a member of the 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 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.

8.3 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 (and their caregivers) detailing: 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

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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.

8.4 Screening Visit

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 study team will demonstrate the study home monitoring system (again), check inclusion and exclusion criteria as far as possible, record relevant current medication, and details of medical and heart failure history. Participants who appear to be eligible based on this initial screening 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. At the screening visit a blood test will be taken to check blood electrolytes, haemoglobin, renal function and brain-natriuretic peptide (BNP) level, unless these tests have been performed recently (within the last 30 days). The blood sample will be sent to the local laboratory for analyses and review during the run-in phase.

8.5 Run-in Phase

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 2 home monitoring system. Their GPs, heart failure nurses and cardiologists (as applicable) will be informed about their potential 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. During run-in, remaining information for full assessment of patient eligibility will be obtained. These include the result of the blood investigations, collection of recent echocardiogram and ECG reports, and review of 3G mobile or WiFi network connectivity for the participant.

The central clinical management (CCM) team, supervised by a consultant cardiologist and assisted by computer-guided decision support, will further develop and record an individualised clinical management plan prior to randomization. This plan will reflect the optimal guideline recommended therapy, as defined by the NICE guidelines for management of patients with chronic heart failure and other relevant source of evidence-based management. The management plan will consider patient's clinical characteristics, such as the type of heart failure (preserved vs. reduced ejection fraction), co-morbidities (e.g., atrial fibrillation or diabetes), information obtained from self-reported screening questionnaires (e.g., possible depression or reduced physical activity) and current treatment and any known drug intolerances. Through systematic screening, clear management targets will be defined.

8.6 Completion of Baseline Assessment and Randomisation

Participants who are potentially **eligible** based on the information obtained during run-in phase will be contacted over the phone and asked if they have experienced any serious adverse events (SAEs) since screening visit, if they are still willing to continue their participation in the study, and if they have any technical questions in regard to the home monitoring equipment. If participants report issues using the home monitoring equipment that cannot be resolved over the phone, a home visit will be arranged.

Eligible and consenting participants will be randomised to the study intervention or control arm by the central research staff within a working day after the telephone call or 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[16]) and study site.

For participants who are clearly **ineligible** based on the information obtained during run-in phase, a home visit will be arranged to explain the reason for ineligibility to the participant and to retrieve the

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SUPPORT-HF 2 equipment. The reason will be recorded for future tabulation. In addition, participants rendered ineligible during follow-up phase will be asked whether they consent to a 6-monthly telephone follow-up and/or indirect follow-up through EHR integration. The information from a suitable sub-group of these non-randomised patients ('usual care' group) will be used to assess the possible impact of the active control on outcomes (see section NON-RANDOMISED 'USUAL CARE' CONTROL GROUP).

8.7 Blinding and Risk of Bias

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. The following procedures will be set-up to reduce the risk of bias as much as possible:

Participant blinding: both treatment groups will retain and use the SUPPORT-HF 2 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 2 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.

Blinding of healthcare professionals and trial team: In addition, the trial will restrict access to the information on treatment allocation as much as possible by defining different roles, data access and blinding procedures:

a. Patient Clinical Care (PCC) team and Local Research (LR) team: the patient's usual clinical care team, such as his GP, community heart failure nurse and consultant cardiologist at the local hospital, as well as the local research team, such as the local recruitment and follow-up nurse, will have access to their patient's basic medical information collected from the SUPPORT-HF 2 system (such as symptoms, BP and weight recordings) but not the treatment allocation. The type and format of the patient information accessible to them will be exactly the same for every patient independently of their treatment groups.

b. Central Clinical Management (CCM) team: the SUPPORT-HF 2 central clinical management team, consisting of heart failure nurses and consultant cardiologists, will have access to the full medical data and treatment allocation of every patient in the study, since this is necessary for them to provide the study intervention. However, to reduce the risk of bias, individualised management plans will be developed prior to randomization.

c. Technical Administration Team: the 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), however they will be blinded to any personal patient information (such as name or NHS number).

d. Statistical Trial Evaluation: both for the formative evaluation, for iterative adaption of the monitoring and management system, as for the summative evaluation of intervention effect, knowledge of treatment allocation is important. Hence the evaluation team will have access to participant's treatment allocation but will be blinded to any personal patient information (such as name or NHS number).

e. Trial Administration Team: all other members of the study team who require access to study data, such as the trial administrators or local research nurses will be provided with a restricted access, blinded to any personal patient information (such as name or NHS number) as well as 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 decision document in APPENDIX B: IMPLICATIONS OF ACTIVE VS USUAL CARE CONTROL summarises, on balance, the advantages of this approach appear to outweigh its disadvantages in SUPPORT-HF 2. In addition, participants who have been rendered ineligible

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because of technical issues (e.g., no internet or 3G access) will act as a 'usual control' group to investigate whether active control has any substantial impacts on clinical endpoints.

8.8 Study Procedures during Follow-up

In addition to diary questionnaires, participants in both study 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, as well as their experience in using the system (APPENDIX A: SCHEDULE OF PROCEDURES). For those reporting SAEs (see section "safety reporting") and for those who have not used the system for some time, complementary telephone assessments for collection of 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.[17] In addition to these active monitoring procedures, the SUPPORT-HF 2 tablet will passively collect information on timing and usage of the SUPPORT-HF 2 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 team for any questions and comments that they may have in relation to the use of the equipment. In addition, the tablet computer will allow patients and their caregivers to contact the study team, either by writing a short message or by pressing a 'request for call back' button.

8.9 Subsequent Visits

After the baseline visits, 3-monthly telephone calls will take place to collect information on patients' medication, adverse events and potential blood test results. After 6-months of follow-up, patients will be contacted by telephone and given the opportunity to remain under active follow-up until the trial end (provided the timing and resources allow this), or to discontinue further active follow-up. For those patients who prefer to discontinue their active follow-up in the study, the 6-months visit will be their final visit and the SUPPORT-HF 2 study system will be collected. For those patients who wish to remain in the study, the 6-month assessment will take place over the phone or at home, and a final visit will be scheduled for the trial close-down phase. This procedure allows for (i) a consistent trial evaluation of all patients at 6-months and (ii) the trial to benefit from the additional information and experience gained from patients with a longer follow-up period.

8.10 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 continued follow-up information through telephone calls or record linkage during the trial period and after trial completion through record linkage only. 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 trial administration system. 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.

The patients' GPs, heart failure nurses and cardiologists (as applicable) will be informed about their patients' discontinuation from the study.

8.11 Definition of End of Trial

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

9 INTERVENTION DESCRIPTION

9.1 SUPPORT-HF 2 Platform

The SUPPORT-HF 2 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. 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 or University 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, as described in the following sections.

9.2 Enhanced Self-Management

Figure 1 provides an overview of the system architecture in 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 will be assessed through validated questionnaires (EQ-5D, MLHFQ, PHQ-2 and PHQ-9) at the screening visit, then at 3-month intervals and at the end of the study.

Integration with clinical pathways: The home monitoring data will be linked to participants' EHR for retrieval of additional data 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.

Individualised clinical management plan: the management plan recorded pre-randomization will not be accessible by the study team during the course of the study and will be used for final trial evaluation only.

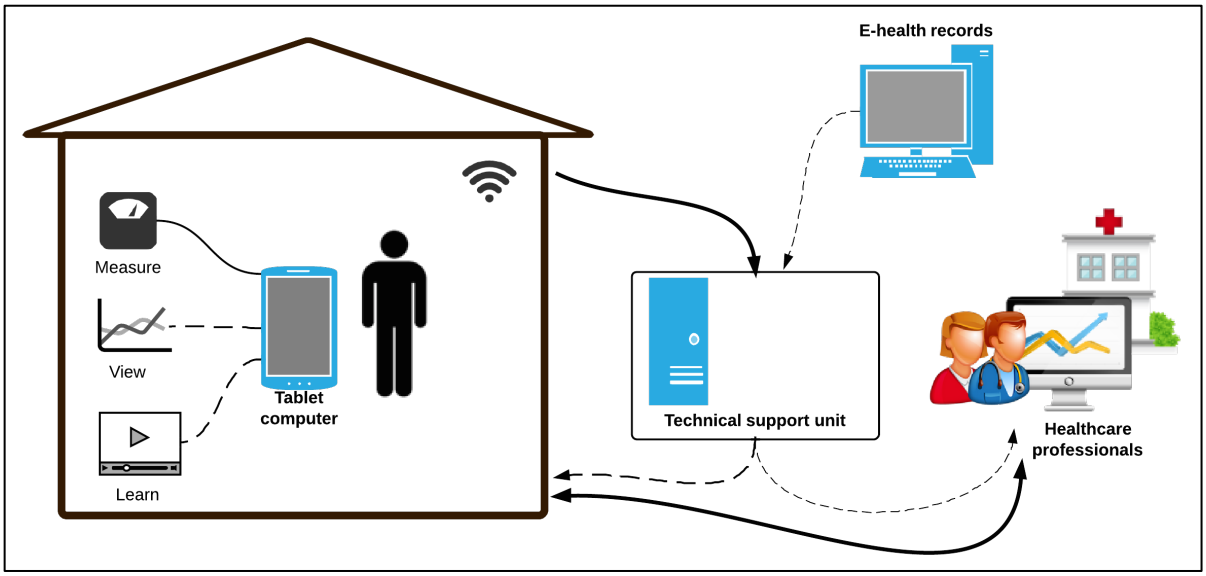

Figure 1: System features of the Enhanced Self-Management group

Feedback and self-management support:

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- **Educational material:** Participants are able to 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.
- **Readings**: Participants are able to view their previous readings, displayed in a graphical format. 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.
- **Contacting the study team**: Participants will also be able to contact the technical and administrative team for any study-related questions that they may have by pressing a 'request for call back' button. This will trigger an email or text message 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.

9.3 Supported Medical Management

Figure 2 provides an overview of the system architecture in the Supported Medical Management group.

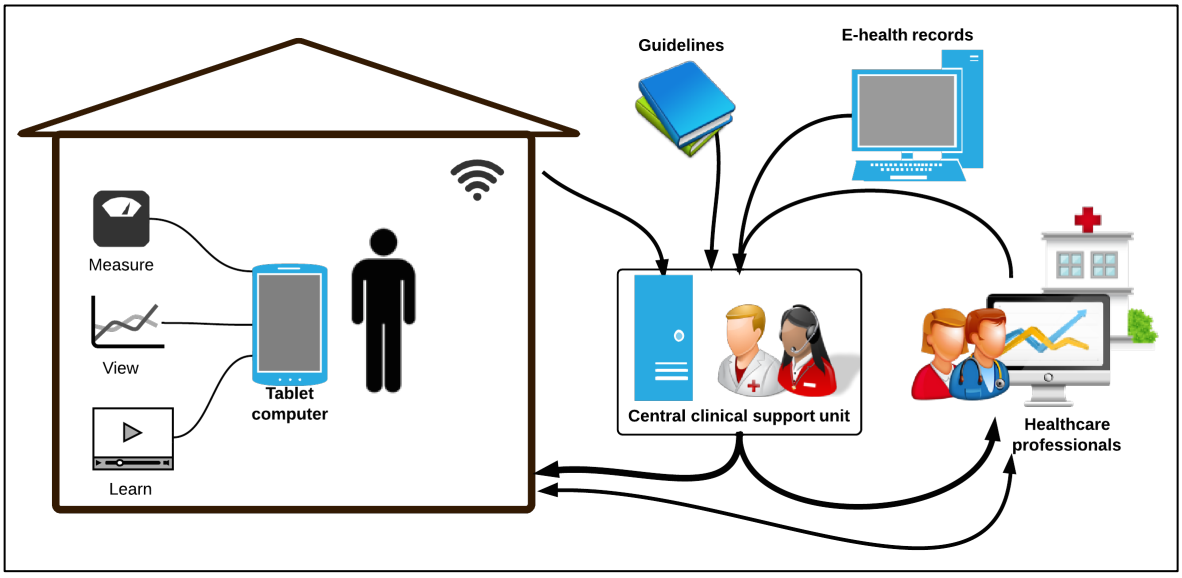

Figure 2: System features of the Supported Medical Management group

Measurement: Participants allocated "Supported Medical Management" group will be provided with exactly the same equipment and will start with exactly the same monitoring scheme. Additionally, patients in the "Supported Medical Management" group may be prompted for additional questions, via the tablet PC application, to gain more information about their health status or clinical management.

Clinical Management System: The core of the intervention is an integrated central clinical management (CCM) unit consisting of a cardiologist and heart failure nurses, supported by an advanced clinical decision support system as well as by technical and administrative personnel. The SUPPORT-HF 2 clinical management system relies on the following main components:

- **Integration with clinical pathways**: The CCM 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.
- **Risk monitoring and prediction**: the SUPPORT-HF 2 clinical decision support system 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

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the EHR and clinical practice guidelines to generate a continuously updated risk prediction and clinical decision support.

- **Individualised clinical management plan**: the management plan, established in accordance with clinical guidelines pre-randomization, will be detailed and adapted to patients' specificities and will guide the CCM team in the clinical management of patients.

The system also offers the flexibility of including local clinical pathways and/or a more active involvement of local care teams in patient care, if desired by the local teams.

Feedback and self-management support:

- **Educational material:** The CCM unit will use the baseline information from each participant to 'personalise' the educational material. Based on participant's health status, type of heart failure, medication plan or co-morbidities, certain types of educational material will be activated or deactivated.
- **Readings**: 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. These may include information about risks as well as health related recommendations.
- **Medication**: Patients will have access to their current list of medication in a simple overview on the tablet PC. They will be able to inform the study team of changes in their medication by pressing a button. The study team may also ask patients about their medication changes by prompting a question on the tablet PC on a regular basis.
- **Clinical management**: Patients will be ranked according to their need for monitoring and change in their management plan. Those who are at high risk of clinical deterioration will be flagged for more intensive review of their measurements 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 (or in case of diuretics down-titration) under monitoring of haemodynamic status (blood pressure and heart rate) and renal function according to clinical guidelines. The central clinical management (CCM) team will review the system-generated alerts and decide on the most appropriate actions, such as recommending changes in patients' medication plan and requesting blood tests. The CMM's clinical recommendations will be communicated to participants as well as their healthcare professionals.
- **System adherence**: 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.
- **Contacting the study team**: Participants will also be able to contact the technical and administrative team for any study-related questions that they may have, either by writing a short message or by pressing a 'request for call back' button. Patients will also be able to view their previously received and sent messages.

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.

10 NON-RANDOMISED 'USUAL CARE' CONTROL GROUP

Additionally to the study intervention, we will follow-up patients who drop out during run-in to act as a 'usual care control' group. Because the clinical characteristics of this non-randomized group is likely to differ from randomized participants, we will select a subgroup of these excluded patients (e.g., those

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that dropped out because of technical connectivity issues) and check their baseline characteristics with randomised participants before any analysis is made.

These patients will not have access to study equipment and will not receive any medical intervention from the study team. They will be asked for their permission to access their health records, and to be contacted by phone every 6-months to obtain additional medication information (adverse events and prescribed medication) and quality of life assessment (EQ5D, PHQ-2, PHQ-9, and MLWHF) from them. These patients will be presented the 'Usual Care Group Participant Information Letter' and consenting participants will be asked to personally sign and date the latest approved version the 'Usual Care Group Consent Form'. A copy of the signed Informed Consent will be given to the participant. The original signed form will be retained at the trial site.

11 SAFETY 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

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 trial management system 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 adverse events 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) will be directly reported by the participants with the use of the home monitoring equipment or through the planned visits. Information on healthcare utilization and medical investigations will be captured directly through EHR.

12 STATISTICAL ANALYSIS

There will be 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. This is to allow continuous adaptation of the intervention components (formative evaluation) and contents without compromising on the rigour of randomised comparisons (summative evaluation). A more detailed Statistical Analysis Plans will be developed. A brief overview of these evaluations 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,

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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.

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 internal pilot trial is "optimal medical therapy" defined as treatment consistent with 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 and the primary analysis will be the difference in percentage opportunity scores between the treatment arms. This will be tested at the two-sided 5% significance level. 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,[18] 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 across the two treatment arms combined. Thus, the opportunity score (OS) is:

$$OS_{\mathrm{i}} = w_{\mathrm{s}} \frac{t_{\mathrm{si}}}{T_{\mathrm{si}}} + (1 - w_{\mathrm{s}}) \frac{t_{\mathrm{di}}}{T_{\mathrm{di}}}$$
$$OS_{\mathrm{c}} = w_{\mathrm{s}} \frac{t_{\mathrm{sc}}}{T_{\mathrm{sc}}} + (1 - w_{\mathrm{s}}) \frac{t_{\mathrm{dc}}}{T_{\mathrm{dc}}}$$

i being the intervention arm, and c the control arm
s being patients with systolic dysfunction and d patients with no systolic dysfunction
w_s being the proportion of patients with systolic dysfunction
T being the sum of total eligible indicators for all patients who began 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[19] as well as clinical practice guidelines for management of major co-morbidities in patients with heart failure (atrial fibrillation, ischaemic heart disease, hypertension, depression). At the final evaluation, the latest treatment plan 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

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Given that many patients with optimal medical therapy will be excluded from participation into the trial and because gaps in the system for optimisation of medical therapy in the community, we assume the opportunity score in the control group to be 0.7 (i.e., at the end of the study, participants will have received 70% 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 15% between the intervention and control arms to be realistic. With these assumptions, randomisation of 161 participants per trial arm will provide 90% power (2α=0.05) to detect an absolute 15% difference in the primary outcome between the trial arms. To take account of attrition, we estimate that a total 350 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,[20] randomisation of 350 patients will also have > 90% power at two-sided alpha 0.5 to detect a 4 point difference in the subscale.

13 EVALUATION OF SECONDARY OBJECTIVES

The secondary objective of the trial is to assess the possible immediate extension of the study into a large-scale trial with clinical outcomes and cost-effectiveness as its primary outcomes. The Trial Steering Committee will be provided with the following in order to be able to make a decision about trial extension:

- site activation status, participant recruitment rates, blinded event rates and success rate in IT integration with EHR (to decide on design or conduct issues)
- drug management in the intervention arm (to decide on fidelity of the intervention as intended)
- resource utilization (to decide on adequacy of resources to extend the trial)
- impact on death and hospitalisation (to judge the interventions potential to show beneficial effects)

The extended clinical outcome trial aims to investigate whether the intervention leads to reductions in the risk of hospitalisation and death, and improvement in health-related quality of life. Death and hospitalisations will be captured through direct linkage of the records with EHR and through patient interviews and questionnaires during the course of the study. Hospitalisation and death will be primarily measured as the percentage of days spent alive and out of hospital.[21,22] The percentage 'days alive and out of hospital' (%DAOH) endpoint incorporates the components of days in hospital (including repeat hospitalisations), days alive and not in hospital, and days dead into a single measure over whole study follow-up period. This outcome measure has been developed to address the issue of repeat hospitalisations for all causes, but it is limited in its ability to weight the relative importance of deaths vs. repeat hospitalisations and it tends to give much greater weight to early deaths than multiple recurrent hospitalisations followed by death very late in follow-up. To overcome this issue, we will also use the so-called 'win-ratio', as described recently, in secondary analyses.[22,23]

One potential risk of unblinded interim analyses of clinical endpoints during or at the end of the pilot phase is the possibility of type 1 error. In order to minimise such risks, we will adopt the recommended trial stopping rules by Haybittle-Peto, which requires "proof beyond reasonable doubt" that the trial intervention is clearly beneficial, or clearly harmful. A difference of at least 3 standard deviations in an interim analysis of mortality or major morbidity will thus be needed to justify halting, or modifying, the study prematurely. This criterion has the practical advantage that the exact number of interim analyses is of little importance.

14 HEALTH ECONOMIC EVALUATION

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The pilot study on its own will not be sufficiently large or of long enough duration to allow a full economic evaluation. For the full trial, we intend to include both 'within-trial'-cost-effectiveness analysis and a modelled economic evaluation according to published guidelines.[24] For the pilot study, we will capture the following information to provide preliminary data on likely cost-effectiveness.

Costs of the intervention: We will capture the costs of the SUPPORT-HF 2 monitoring system, including the costs of hardware, software, server integration, baseline training visit and educational materials, time provided by clinical support unit cardiologists and nurses in providing monitoring and advice. We will exclude any costs associated with evaluation of the clinical trial but include all resources needed to reproduce the program.

Healthcare utilisation: Patients' healthcare utilisation (doctor visits, medication use, diagnostic tests, use of emergency departments, hospitalisations) will be determined through EHR linkage. Information from non-randomised 'usual care' control group will be used to assess the validity of healthcare utilization estimates in the 'supported self-management group'. Cost weights for diagnostic and related group (DRG) codes for hospitalisations will be obtained from NHS Reference Costs.[25] Quality of life will be assessed at baseline, then at the end of the pilot study, using the (EQ-5D); utilities will be calculated using the UK scoring algorithm. At the end of the pilot phase we will further compare the differences in utility scores as obtained from the EQ-5D questionnaire at the beginning of the study and after six months vs indirect estimation by applying the NYHA class-specific disabilities as reported by the Global Burden of Disease Study 2013 Collaborators.[26]

These data will allow us to estimate the cost per patient in delivering SUPPORT-HF 2, whether use of the monitoring system results in any cost offsets (i.e., reduction in other healthcare utilization) and whether there are any apparent differences in patient reported quality of life.

15 DATA MANAGEMENT

15.1 Source Data

Source documents are where data are first recorded, and from which participants' medical data are obtained. These include, but are not limited to, hospital or GP records (e.g. laboratory data, hospitalisation episodes or current medication), home monitoring diaries, and correspondence with study staff. Case Report Forms (CRF) 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, the participant will be referred to by the trial participant number/code, not by name. However, the clinical management team must have access to participant name in order to be able to communicate management plans with other non-study clinicians.

15.2 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.

15.3 Data Recording and Record Keeping

A schematic overview of the trial data architecture and management system is provided in Figure 3.

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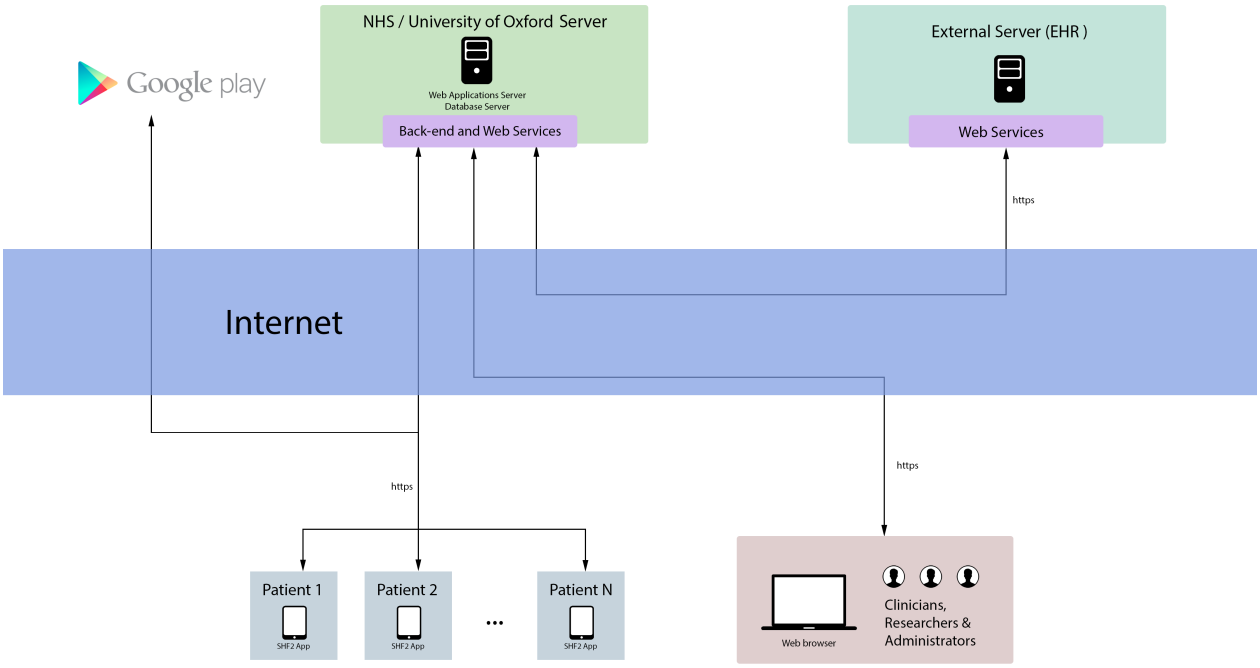

Figure 3: Trial data architecture and management system

The SUPPORT-HF 2 study IT system will consist of custom-written applications as well as commercially available and open-source applications.

The SUPPORT-HF 2 data management system is designed as a database and web applications servers located on a secure firewall protected NHS or University server. The web applications will allow for secure data transmission from external EHR source server, electronic case report forms as well as de-identified measurements from study tablet computers used by the patients.

Tablet computers will have a custom-written (android and/or iOS) application for data acquisition from sensors or monitors and for data exchange with the secure web services. Tablet computers will not store nor transmit any patient identifiable information. All data on the tablet computers will be securely transmitted wirelessly to the SUPPORT-HF 2 study server.

The back-end system will be accessible via a secure web interface by the study team according to allocated user rights. A user, roles and access management system will allow access restrictions as described in the trial procedures. These foresee that patient identifiable information can only be accessed by authorised clinical users.

The back-end system will intermittently extract data from EHR databases in an automatic manner. Such data will include laboratory results, PACS or other imaging information, hospital admission episodes or clinic visits, and medication prescriptions.

Electronic case report forms may be used to enter patient identifiable information such as contact details and medical information (eg. for SAE reporting or updated medication) and will be transmitted securely to the study back-end system. Any changes to the data will require the users to enter their credentials as an electronic signature.

16 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.

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17 TRIAL STEERING AND DATA MONITORING COMMITTEES

17.1 Trial Steering Committee

The SUPPORT-HF 2 study will be overseen by an independent Trial Steering Committee, whose role will be to guide the research agenda, advise on the plan of investigation, and monitor the execution of the project. The Steering Committee will meet about two to three times annually in person with some email and telephone communication in between.

The Steering Committee will be composed of the following members:

- Professor Frances Mair (Professor of Primary Care Research and Head of General Practice and Primary Care, Institute of Health and Wellbeing at the University of Glasgow), Chair of the SUPPORT-HF 2 Steering Committee;
- Professor John McMurray (Professor of Medical Cardiology in the Institute of Cardiovascular and Medical Sciences at the University of Glasgow);
- Dr Nicola Greenlaw (Statistician, the Robertson Centre for Biostatistics, University of Glasgow).

The members of the Steering Committee may change with the approval of the Steering Committee Chair.

17.2 Data Monitoring Committee (DMC)

A DMC will be established and will meet once annually or deemed appropriate by the Chairman of the DMC, usually before the TSC meetings. An unblinded analysis of all adverse events and other study outcomes will be provided in strict confidence to the Chairman of the Data Monitoring Committee. In light of these analyses and any other information considered relevant, the DMC will advise the TSC if, in their view, the randomised comparisons in the study have provided **both** (i) "proof beyond reasonable doubt" that for all, or some specific types of, patients prolonged the trial intervention is clearly beneficial, or clearly harmful; **and** (ii) evidence that might reasonably be expected to influence materially the patient management of many clinicians who are already aware of the results of other trials. Appropriate criteria of proof beyond reasonable doubt cannot be specified precisely, but in general a difference of at least 3 standard deviations in an interim analysis of mortality or major morbidity would be needed to justify halting, or modifying, the study prematurely. This criterion has the practical advantage that the exact number of interim analyses is of little importance. With the DMC advice, the TSC can then decide whether to modify the study, or to seek additional data. Unless this happens, the TSC, collaborators, study patients, and all study staff (except those who provide the confidential analyses to the Data Monitoring Committee) will remain blind to the comparative results until the end of the study.

18 ETHICAL AND REGULATORY CONSIDERATIONS

18.1 Declaration of Helsinki

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

18.2 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.

18.3 Participant Confidentiality

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The trial staff will ensure that the participants' anonymity is maintained. With the exception of the clinical management system, 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 anonymised as soon as it is practical to do so.

18.4 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.

18.5 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.

19 FINANCE AND INSURANCE

19.1 Funding

The SUPPORT-HF 2 is supported by an NIHR HS&DR grant, a NIHR Career Development Grant to the CI and NIHR Oxford BRC funding.

19.2 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.

20 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.

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22 APPENDIX A: SCHEDULE OF PROCEDURES

Procedures	**Screening** (at home or clinic)	**Baseline** (telephone call)	**Follow-up for Randomized Patients**			**Non-randomised control**
			Follow-up (telephone call) Minimum 3-monthly	**6-month** (at home or clinic)	**Final** (at home or clinic)	**Follow-up** (telephone call 6-monthly)
Informed consent	x	x				
Demographics and medical history	x					
Current medications	x	x	x	x	x	x
Biochemistry, renal function and BNP *	x		(x)	x	x	(x)
Eligibility assessment	x	x				
Randomisation		x				
Usability assessment		x		x	x	
Adverse event assessments		x	x	x	x	x
Quality of life assessment (EQ5D, MLWHF)	x		x	x	x	x
Initial depression screening (PHQ-2)		x	x	x	x	x
Detailed depression screening (PHQ-9)**		(x)	(x)	(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.

** Detailed depression screening will only be performed on patients have scored positively on the initial depression screening (PHQ-2)

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23 APPENDIX B: 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 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 acquisition for behavioural data (e.g. usage of the system)			
	Use of retrieved self-monitoring data in the control arm for validation of the risk prediction model			
☐	**Impacts of the study findings**			☐
	Emphasises that its not the equipment but the software and processes that are active ingredients of the intervention		Some patients in the control arm may become dissatisfied with the limited support that they are receiving during the course of the study	
	Study findings will be study scientifically more robust		Active control makes the findings less policy-relevant (but can be addressed in subsequent sensitivity analyses)	
☒	**Overall decision**			☐

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