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A study of Physical Activity paTTerns and major health Events in older people with implantable cardiac devices

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CI: Dr Adam Greenstein

PI: Dr Joanne Taylor

Sponsor: University of Manchester

Host: Manchester University NHS Foundation Trust

MANCHESTER 1824

The University of Manchester

Study Title

A study of Physical Activity paTTerns and major health Events in older people with implantable cardiac devices (PATTErn)

Chief Investigator

Dr Adam Greenstein (AG), Clinical Senior Lecturer, Division of Cardiovascular Sciences, University of Manchester

Principle Investigator and Researcher

Dr Joanne K Taylor (JKT), MD student, University of Manchester, Clinical Fellow, Manchester University NHS Foundation Trust

Supervisors

Dr Adam Greenstein (AG), Clinical Senior Lecturer, Division of Cardiovascular Sciences, University of Manchester

Professor Niels Peek, (NP), Professor of Health Informatics, University of Manchester

Dr Fozia Ahmed (FA), NIHR CRN Greater Manchester Cardiovascular Speciality Lead, Consultant Cardiologist, Central Manchester University Hospitals

Additional Members of the Reporting Team

Neil Pendleton (NP), Professor of Medical Gerontology, Division of Neuroscience & Experimental Psychology, University of Manchester

Dr Nathaniel Hawkins (NH) , Clinical Assistant Professor, Heart Failure and Cardiac Electrophysiology, University of British Columbia

Sponsor

The University of Manchester (UoM)

Sponsor contact: Ms Lynne Macrae, Faculty Research Practice Governance Co-ordinator

Address: Faculty of Biology, Medicine and Health, 1.21a Simon Building, University of Manchester, M13 9PL

Email: FBMHethics@manchester.ac.uk

Telephone: 0161 275 5436

Host

Manchester University NHS Foundation Trust

Host Contact: Ms Sarah Mackie, Senior clinical trials co-ordinator

Address: Research Office, Manchester Heart Centre, Manchester Royal Infirmary, M13 9WL

Email: Sarah.Mackie@mft.nhs.uk>

Telephone: 0161 276 3336

Funder

Medtronic Limited

Sponsor contact: Mark Elsey, Senior Finance Director, UK, Ireland and NBP

Address: Building 9, Croxley Park, Hatters Lane, Watford, Herts, WD18 8WW

Telephone: 01923 212213

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Supporting Documents

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- Study participant questionnaire
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- Consent withdrawal form
- HRA schedule of events form
- HRA statement of activities form
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- IRAS form
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- Funding letter - Medtronic
- Panman form
- Chief Investigator's CV
- Principle investigator's CV

Abbreviations

.pdd	programmer desktop document
ADL	Activities of daily living
AF	Atrial fibrillation
CI	Confidence interval
CIED	Complex implantable electronic device
CF	Consent form
CRF	Case report form
CRT	Cardiac resynchronisation therapy
CRT-D	CRT with defibrillator
CRT-P	CRT with pacemaker
CtC	Content to contact
CWF	Consent withdrawal form
DARS	Data access request service, NHS Digital
DMP	Data management plan
DOA	Date of hospital admission;
DOEDA	Date of emergency department attendance
DOD	Date of discharge
eGFR	Estimated glomerular filtration rate
GCP	Good Clinical Practice
GP	General Practice
HCU	Healthcare utilisation
HeRC	Health eResearch Centre, University of Manchester
HES	Hospital episode statistics
HF	Heart failure
HR	Hazard ratio
ICD	Implantable cardiac defibrillator

IL	Invitation letter
IRAS	Human Research Authority Integrated Research Application System
IT	Information technology
LOS	Length of stay
m	Meter(s)
MDPA	Mean daily physical activity
MFT	Manchester University NHS Foundation Trust
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NHS	National Health Service
ONS	Office of National Statistics
PA	Physical activity
PI	Principal investigator
PIS	Patient informed sheet
RAPA	Rapid Assessment of Physical Activity
RCT	Randomised control trials
SF-36	Medical Outcomes Study Questionnaire Short Form 36 Health Survey
SPQ	Study participant questionnaire
SPN	Study participant number
UoM	University of Manchester
QOL	Quality of life

Summary

Background

Expanding clinical indications and an aging population have resulted in an increased number of implanted cardiac devices (CIEDs) being used worldwide. CIEDs record patient activity (PA) on a daily basis in addition to other physical parameters. Despite routine use in clinical practice, the utility of integrated PA diagnostics to monitor health in an older population remains relatively unexplored. This novel, interdisciplinary study aims to utilise easily accessible data from CIED downloads to improve our understanding of the relationship between PA and major health events (as measured by non-elective hospital attendance episodes) in an older population with heart disease. The PATTErn study will recruit 150 people aged ≥60 years with a CIED from the Manchester University NHS Foundation Trust over an 18-month period. Their observational data will be analysed to explore longitudinal PA patterns, correlations with markers of physical ageing such as frailty, and the relationship between PA and non-elective hospital attendance episodes (NEHAs). In essence, this study will bring together expertise in Geriatric Medicine and Cardiology, to exploring how this 'non-cardiac' device data correlates with health status.

Results will directly guide local pilot studies testing the impact of personalised, actionable clinical summaries from CIED data downloads. It will also have wider impact across the research community, accelerating our knowledge of the interaction between PA and health outcomes in an older cohort. This may lead to future projects looking at the use of this data to proactively identify older people at immediate risk of hospitalisation.

Research question

What are the normal variations in daily PA in later life, and how does PA associate with major health events?

Aims

1. Describe the relationship between PA and NEHAs in an older CIED cohort
2. Describe daily variability of PA in an older CIED cohort
3. Describe the relationship between PA and NEHAs, and examining whether frailty moderates this relationship

4. Confirm/refute the clinical observation that a drop in PA tends to precede episodes of NEHA in later life, and if so, evaluate predictive value

Method

Study Type: observational, investigator led

Study Design: observational model: cohort (retrospective)

Population: 150 people over 60 years of age with a Medtronic CareLink® compatible CIED in situ recruited from the Manchester University NHS Foundation Trust, England, UK

Data collection: daily PA measures, demographic details, co-morbidity status, physical frailty assessment, functional status, quality of life (QOL) and NEHA data

Consent: for participation in the study, physical frailty assessment, additional collection of retrospective CIED data, and access to electronic patient records

Data sources: CIED downloads, self-report questionnaire, physical measurements (height, weight, hand grip strength, gait speed), electronic hospital records, HES (hospital episode statistics) data

Results analysis: data will be analysed to investigate: daily PA variability; the association between PA and NEHAs, and the impact of frailty on PA patterns

Scientific and medical opportunities

This study will collect a unique set of new data for analysis. Combining expertise in Geriatric Medicine and Cardiology, this work will aim to provide a scientific basis for some of the fundamental assumptions made regarding health behaviours in later life. Little is known about normal day-to-day fluctuations in PA in an older population. This objective data will shed light on these patterns, and the temporal relationship between PA and NEHAs. Not only will this enhance our clinical knowledge, but it will provide the opportunity to develop proactive monitoring systems – potentially using PA as a proxy marker of health in certain older patient groups.

Expected outcomes

This study expects to find that NEHAs are commonly preceded by a demonstrable acute decline in PA. Various models will be tested to demonstrate predictive validity. This association is expected to vary by patient sub-groups defined by baseline health status (co-morbidity burden, degree of frailty), and demonstrated underlying activity pattern.

Further avenues for research

Following on from this study, we hope results will guide the development of accurate, clinically meaningful early warning systems for older people at risk of physical decline using accelerometer data. Older people with CIEDs in situ will act as a 'testing ground' for this research, using device download data. Avenues for further research will be two-fold; improved specificity of pre-existing heart failure decompensation alert systems using PA data processing techniques, and the creation and pilot testing of personalised, actionable clinical summaries from CIED data. More widely, if this study finds PA is a clinically useful marker of health in this 'test' population, there is scope to expand this work into other older populations at risk of decline and dependency using external wearable accelerometry e.g. post hospital discharge.

Rationale/Background

Context

Older people are the biggest users of both emergency medical and social services in the UK (1). This is not simply due to a higher prevalence of disease; rather the impact of age-associated morbidity on physiological and functional coping mechanisms. This vulnerability to functional decline or 'reduced mobility' in the face of seemingly minor stressors is now recognised as the frailty syndrome (2). This new conceptual framework has raised the possibility that physical activity (PA) could be used as a proxy for health status in older age. PA is now easily measureable in real-time using ubiquitous technologies such as smart watches, paving the way for continuous monitoring systems. Predicting impending 'dependency crisis' triggered by frailty or ill health could help target evidence-based upstream intervention, shown to prevent functional decline (3), falls (4, 5) nursing home admissions (4, 6, 7) and unnecessary hospitalisation (4, 8-11), particularly in those with chronic diseases such as heart failure (12, 13).

Although these systems have huge potential to revolutionise the care of older people in the community, they remain in their infancy, hindered by poor understanding of the normal patterns of daily activity in older age. Obligate data from complex implantable electronic devices offers a unique opportunity to study the temporal patterns of functioning and frailty in a real-world setting.

CIED cohort

Every day, a huge volume of physiological data, including daily PA, is routinely collected by most modern cardiac implantable electronic devices (CIEDs). These devices are fitted in patients with cardiac conduction disorders and/or heart failure (HF). The average age of a patient undergoing implantation of a CIED in the UK is approximately 70 year old (14, 15). Older people with CIEDs are a cohort of patients with a particularly high risk of clinical frailty, hospitalisation and mortality (16-19). This therefore makes an ideal population to study PA patterns and temporal relationships with major health events.

CIED remote monitoring

Modern CIEDs continuously collect data for a host of physiological parameters relevant to cardiac function, including; heart rate, rhythm and variability, thoracic impedance, pacing time and PA. This data is stored within the device until it is 'downloaded' for analysis (for up to 14 months). For example, the Medtronic CareLink® Network allows patients to manually download data via a home monitor system as well as automatic programmed downloads ordered by clinicians (usually every 3 months from home, and an annual hospital based CIED check). Reports are then forwarded on to care providers for action. PA is considered 'low' if patients are 'active' (defined as >70 steps/min) for less than 60 minutes over a 1-week period (non-overlapping).

Existing evidence

Algorithms using CIED data to predict impending healthcare utilisation (HCU) have been in existence for a number of years, but are not yet integrated into standard UK clinical practice. The PARTNERS-HF study (20) tested a prediction algorithm based on a combination of 8 parameters (AF duration, ventricular rate during AF, fluid index, patient activity, night heart rate, heart rate variability, % of pacing CRT and ICD shocks) in HF patients with CRT defibrillators. Patients with parameters outside the norm for 2 or more domains triggered an alert for clinical action. Cowie *et al.* 2013 expanded the PARTNERS-HF dataset, totalling 921 HF patients, mean age 67-68 years (21). 30-day HF hospitalisation rates in the high-risk group were 10 times higher than in the low risk groups, HR (hazard ratio): 10.0; 95% CI: 6.4–15.7, P, 0.001. 'Low' versus 'high' PA was the most common domain trigger, contributing to over 80% of high-risk alerts. Low PA as a single domain was associated with a 2-3 fold increased risk of HF hospitalisation (HR 2.5, P<0.001).

Although these studies have produced promising results, a recent review has highlighted that the predictive accuracy of PA in isolation remains poor (22). Trajectories have not been analysed, 'normal' remains unclear, and there has been no evaluation of the impact of ageing or frailty. Studies have also taken a narrow approach to data collection and outcome measures, capturing episodes of hospitalisation triggered by HF decompensation only, and death primarily due to HF. Bearing in mind people living with HF have on average four additional comorbidities (23), this study will take a holistic approach – measuring all-cause HCU (as measured by non-elective hospital attendance episodes).

Frailty

Frailty describes a state of reduced physiological reserve in older adults (2). Seen as a measure of biological ageing, frailty represents a vulnerability to physical and functional decline in the face of seemingly minor stressors – exemplified by the clinical presentation of 'reduced mobility' (often previously termed 'acopia'). Three broad models of frailty exist in the literature: the phenotypic model, the cumulative deficit model, and pragmatic clinical assessments. The phenotypic model is based on pioneering work by Fried *et al.*, who described the five cardinal syndromic features of frailty: unintentional weight loss, exhaustion, weakness, slow walking speed, and low physical activity (24). This phenotypic model is based upon clinical assessment, and correlates well with markers of functional and physical health (25). Following on from this, Rockwood and colleagues developed the cumulative deficit model – a mathematical index based measure based on the accumulation of 'symptoms, signs, diseases, and disabilities' associated with ageing (26). This has progressed to an electronic frailty index (eFI), - a score based on 36 deficits constructed using over two thousand primary care read-codes (27). This model is population based, calculated remotely. In addition to these two models, a number of validated pragmatic clinical assessment methods exist, for example the Clinical Frailty Scale (28) and the Edmonton Frail Scale (29).

For the PATTErn study, frailty assessments will be based on the Fried phenotypic model. This method was chosen as it demonstrates closest clinical correlation on an individual level, and is the most established in clinical and research practice (30). It also allows for the additional definition of 'pre-frail' i.e. patients at high risk of developing clinical frailty in the near future.

Considerations/Limitations

Accuracy of PA data from CIEDs

A number of reviews have examined the accuracy of various types of wearable activity trackers (31-34). PA is measured in CIEDs using an embedded single-axis accelerometer. Single-axis accelerometers only measure activity performed in the superior/inferior motion, thus are sensitive for postural movements such as walking, but less so for other forms of activity. For this reason single-axis devices may underestimate overall energy expenditure. With regard to accuracy in an older cohort, all activity monitors tend to be less accurate in participants with slower gait speed (33). In terms of differentiating 'active' versus 'sedentary' time, single-axis accelerometers have been shown to be accurate even in an older disabled cohort (35). A study by Pressler *et al.* 2013 (36) compared PA measurements from CIEDs with external tri-axial accelerometer in 73 participants (mean age 60±20 years). Correlation between the devices was strong (mean total daily activities, $r=0.64$; $p<0.001$) as was intra-individual correlation in the majority of participants (70%, $r>0.7$, $p<0.05$). However, Bland Altman plot analysis suggested significant variations in total daily activity measurements. Therefore, use of this data for pattern/trend analysis (as in this study) has been shown to be sufficiently accurate, however direct comparison of discrete PA measurements should be made with certain caveats.

Impact of CIED implantation on results

CIEDs include pacemakers, implantable cardiac defibrillators (ICDs), and cardiac resynchronisation devices (CRT). NICE guidelines (National Institute for Health and Care Excellence) recommend CRT device implantation as a *treatment option* for HF patients with prolonged QRS interval on electrocardiogram and an ejection fraction of 35% or less (37). CRTs have been shown to improve symptoms and slow progression of HF in randomised control trials (RCT) (38, 39). The MIRACLE study (38) (an RCT of 453 patients with moderate to severe HF randomised to CRT versus medical therapy) demonstrated CRT patients experienced a median change in 'distance walked in 6 minutes' of +39m at 6-month follow up (median: +39m, 95% CI +26 to +54, compared to control median: +10m 95% CI 0 to +25, where CI = confidence interval). Evidence suggests the additional endurance effect of CRTs is diminished by 12 weeks of implantation (40), thus data from this time period will be excluded from analysis as PA data may not represent normal behaviour. This will also allow time for the

patient to recover from the procedure, and allow the device time to synchronise its settings. It is unclear how pacemaker or ICD implantation would affect PA, however one could expect some positive impact through better control of symptoms, or perhaps a psychological 'safety-net' for a more active lifestyle. Although some devices with tight pacing settings may limit exertion. We expect this impact to be very small.

Validity of frailty assessments

The Fried phenotypic based frailty assessments are well validated in the general population. We estimate over half of the patients recruited into the PATTErn study will have some degree of HF. One domain of frailty that may be less reliable in a HF cohort is weight loss – as this may fluctuate with fluid status. Significant weight loss within the criteria is defined as over 10% body weight in the preceding four years (or a measured BMI < 18.5 kg/m^2). These criteria would not tend to capture patients whom have lost weight simply due to diuresis, therefore we do not anticipate this will alter validity of results. The Fried criteria have been used in a number of studies which include participants with HF (19, 41). The original validation study itself included patients with HF, who represented 4.5% of the original Cardiovascular Health Study cohort (42). Therefore, this assessment has validity in this context.

Generalisability of results

By the nature of this study, participants are limited to those with a compatible CIED i.e. have some form of cardiac disease (the majority HF and/or conduction disorders). Cardiovascular disease is a fundamental pillar of ageing, lying on the spectrum of physiological frailty – inherent, and relevant to all older people (43). Therefore, on balance we do believe this population sample is generalisable to an older population with comparable functional status and degree of frailty. This study will be looking at temporal pattern analysis, using this population as a cohort of older people with a common age-associated long-term condition (heart disease). There is no reason to expect this group of patients would behave any differently with regard to PA and major health events compared with any other older patient group. Therefore we believe these results will be of interest out with the cardiac community.

Sample Size Calculations

Using data from previous analyses (21, 22) sample size calculations have been performed based on the Kesley and Fleiss formulas for 'cohort studies', using exposure = low/decline in PA and outcome = NEHA within 6 weeks. We considered a relative risk (RR) of 2.5-3 to be clinically significant in terms of a PA trigger signifying increased risk of NEHA. Sample size estimate thus = **150** participants (using inputs: 95% significance, 80% power, RR 2.5-3, output: 88 – 198, see *Table 1*).

Table 1: Sample size calculations

Variables	**Option 1**	**Option 2**	**Option 3**	**Option 4**
Two-sided significance level (1-alpha)	95	95	95	95
Power (1-beta, % chance of detecting):	80	80	90	90
Percent of Unexposed with Outcome:	17	17	17	17
Percent of Exposed with Outcome:	43	51	43	51
RR	2.5	3	2.5	3
Ratio of sample size, unexposed/exposed:	4.4	4.4	4.4	4.4
Sample size: Kesley	**133**	**81**	**177**	**108**
Sample size: Fleiss	**145**	**88**	**198**	**121**

The SENSE HF study (enrolling adult patients with chronic, stable HF, 6 months follow-up) captured 224 'unscheduled hospital visits' in 132 patients over 659 patient years, i.e. an annual rate of 34%. (44) Using this as a guide, with a sample size of 150 (150 patient years) we would expect to capture approximately 51 NEHA episodes from retrospective data collection.

Study Objectives

1. Describe the relationship between PA and NEHAs in an older CIED cohort
2. Describe daily variability of PA in an older CIED cohort
3. Describe the relationship between PA and NEHAs, and examining whether frailty moderates this relationship
4. Confirm/refute the clinical observation that a drop in PA tends to precede episodes of NEHA in later life, and if so, evaluate predictive value

Study Design

Type
Observational study

Setting
Manchester University NHS Foundation Trust (MFT). This includes the trust's 2 main sites: Manchester Royal Infirmary and Wythenshawe Hospital.

Duration of Study
18 months

Participants
Inclusion/exclusion criteria are shown below, with reference to *Table 2* that lists compatible CIEDs for this study.

Inclusion Criteria
1. Age 60+ years
2. Functioning CIED in situ for at least 6 months
3. Medtronic manufactured device compatible with CareLink® Cardiac Compass application (platform which measures and stores physiological parameters)
4. Lives in the Greater Manchester area
5. Able and willing to given written, informed consent to enter the study

Exclusion Criteria
1. Faulty or incompatible device
2. Immobile (unable to walk in upright position)
3. Active participant in a clinical trial which does not allow concurrent recruitment into this study
4. People unable to consent in the English language (including the understanding of study literature which is published in English only)

Patients may be entered into registries, observational studies or clinical trials while also participating in PATTErn.

Justification of Study Design

Study design

Research question: what are the normal variations in daily PA in later life, and how does PA change surrounding major health events?

This question is best answered by an observational study, as we are attempting to establish normal patterns of behaviour. Measuring PA using sensor devices allows for the passive collection of objective data. The use of retrospective PA data from CIED devices minimises participation bias (i.e. inadvertently influencing behaviour). Using a cohort of older people with CIEDs limits analysis to a particular cohort of older people, however as explained below in the 'generalizability of results' section, this analysis will still be of great value, and on the whole generalizable to the broader population. Specific considerations related to the PATTErn study are discussed in more detail below.

Selection Bias

Selection bias will be introduced by our inclusion/exclusion criteria and recruitment method in the following ways:

1. Inclusion criteria
    1.1. compatible CIED in situ
        1.1.1. The most frail patients would not be eligible/suitable for CIED implantation
    1.2. Able to provide written, informed consent
        1.2.1. Patients with significant cognitive impairment or physical disabilities affecting ability to sign the consent form will thus be excluded from the study
2. Exclusion criteria
    2.1. immobile (unable to walk in upright position)
        2.1.1. The most frail patients will therefore be excluded
    2.2. People unable to consent in the English language
        2.2.1. This is a practical constraint due to limited funding and resources, but we anticipate will result in reduced representation of people born outside the UK.
3. Recruitment method
    3.1. Consent to contact step
        3.1.1. In inclusion of a CtC step is an ethical requirement given patients will be approached for recruitment remotely. This step adds potential selection bias as we suspect the most 'engaged' patients would fill in and return the forms. We have tried to mitigate this by adding the option of contacting the team via post, email or phone to boast recruitment, and minimise time/effort required to express an interest.

3.2. hospital-based

3.2.1. The most frail patients would be on remote-only follow-up e.g. nursing home resident with very poor mobility

Exclusion criteria have been kept to a minimum to reduce the impact of any selection bias.

Methodology

Study timeline

See *Figure 1* below. This study will have an 18-month recruitment window. Screening and invitation will take place at the beginning of the study, and again at 6 months.

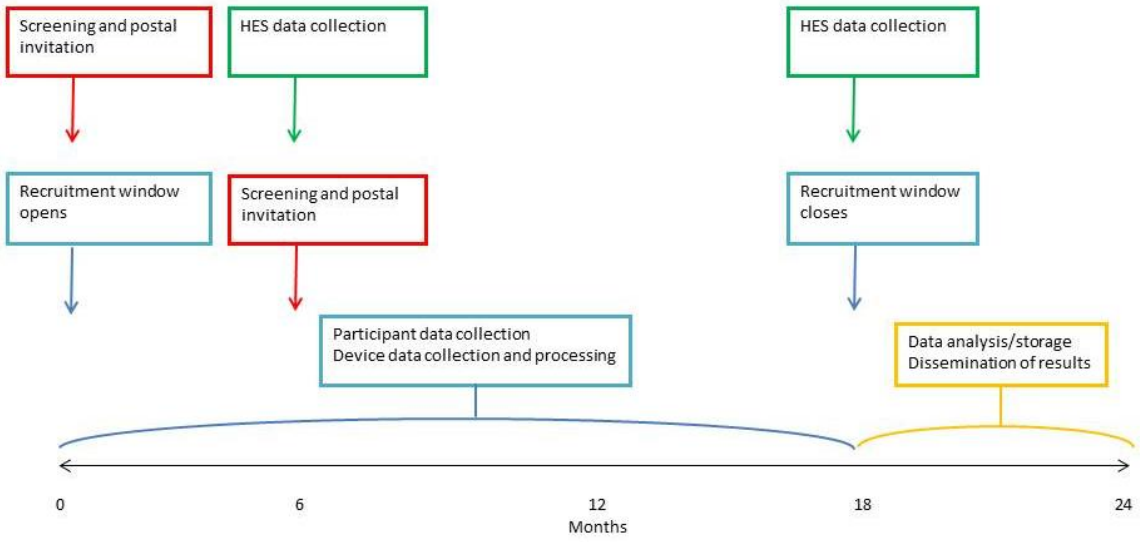

Figure 1: Study timeline

Screening and recruitment strategy

Basic details for all patients registered with the Manchester University NHS Foundation Trust (MFT) are held on an IT system called "Cardex". This system allows for filtering of patients by a variety of

demographics and medical information, thus can facilitate the isolation of all patients on "annual device follow-up" meeting the first four study inclusion criteria. This process will generate a list of patient for postal invite. The screening process will be performed by the care team at the beginning of the study, and will be repeated at 6 months (see *Figure 2*).

All patients identified for postal invite will be sent a 'consent to contact' form (CtC) and invitation letter (IL). Following the second screening process at 6 months, this newly generated patient list will be cross-referenced with the initial screening list to exclude all patients already contacted (i.e. each patient will only be approached once).

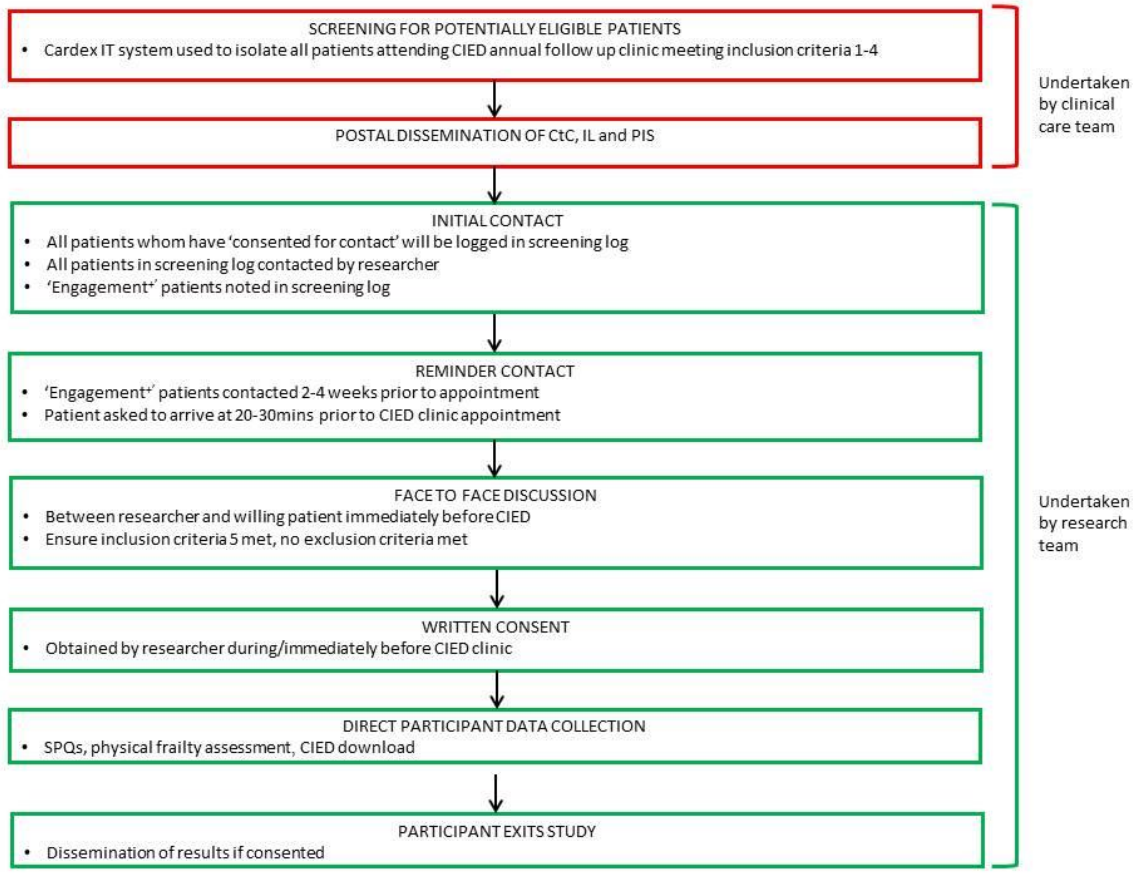

Figure 2: Screening and recruitment flowchart

The CtC form (see supporting documents) will include a phone number for the research team, as well as a slip form for the patient to send back to the research office (a freepost envelope will be

provided). All patients whom indicate they have consented to be contact (either by directly contacting research team or by returning a slip form) will be noted in the screening log ("screening^{+}, CtC^{+}"). The researcher will contact the patient in their preferred method of communication (phone, email, letter) and send out a patient information sheet (PIS). The patient will then be re-contacted (in their preferred method of communication) to establish if they are willing to come in 20-30minutes prior to their scheduled annual device follow-up appointment to speak to the researcher. A further list of "screening^{+}, CtC^{+}, engagement$^{+"}$ patients will be documented in the screening log. A reminder contact will be made 1-2 weeks prior to their scheduled appointment.

The researcher will meet all "screening^{+}, CtC^{+}, engagement$^{+"}$ patients 20-30 minutes prior to their scheduled appointment to allow time to obtain written, informed consent. After a patient has consented to participate, they will be allocated a unique randomly generated study participant number (SPN). A list of consented patients with corresponding study numbers will be kept in the enrolment log in the site file. All study data there in will be identified using this SPN.

18 months has been allocated for recruitment. It is anticipated all recruitment will be undertaken by the PI. Recruitment will not cease once 150 participants have been recruited; rather cease at the end of this 18-month window. This will maximise impact of results and reduce risk to the study if number of captured NEHAs is less than expected.

Rationale for screening and recruitment strategy

Recruitment at annual device follow-up clinic

In order to minimise burden of participation for patients and reduce the cost of the study, we have chosen to recruit patients whilst they attend hospital for pre-scheduled clinic. It is not anticipated this will cause any significant delays/inconvenience for the normal running of the clinic.

Screening by care team

Although the PI is a member of the care team and research team, we have separated out these roles to make it clear how data will be handled.

Consent to contact

Although the PI is a member of the care team and research team, this additional step will ensure the boundary between clinical and research care is maintained.

PIS sent after CtC

The PIS is a relatively long document, thus we have chosen not to send this out with the initial invitation letter. This will reduce printing costs, and potentially avoid patients feeling overwhelmed by paperwork.

Consent

The researcher will obtain explicit, written consent from all participants on entering the study. Consent forms have been produced in line with UoM and MFT guidelines. Reasonable arrangements have been made to minimise exclusion of capacitous, potentially eligible patients.

1. PIS documents will be available in large font format for sight-impaired individuals
2. Participants whom struggle with writing will be given the alternative option of providing verbal responses to the questionnaires (arranged prior to attending appointment to ensure extra time has been allocated, administered by the PI).

Unfortunately due to resource limitation we are unable to provide translators for persons unable to consent in the English language.

Data collection process

CIED data download

CIED downloads will be performed by a trained member of staff (usually a cardiac physiologist or clinician). The operator uses a specialised CIED "programmer" to process wireless transmitted data. A receiver loop is placed over the patient's cardiac device (which sits below the skin and muscle layers on the chest wall). The receiver loop wirelessly connects to the programmer, where physiological and device parameters (alongside patient identifiers) are immediately summarised on the screen. In normal clinical practice, a USB stick is then used to transfer the downloaded *processed* data onto a standard computer for storage. For this study, a copy of *raw* CIED data is required for download in a .pdd (programmer desktop document) file (raw data is not usually required to be downloaded during routine assessments). In order to pseudo-anonymise participant data at source, the researcher will temporarily replace patient identifiers (patient name and patient ID) with the unique SPN on the programmer screen before download. This means all downloaded .pdd files will be pseudo-identified. All .pdd files will be directly downloaded from the programmer into an

encrypted trust USB stick. This will be immediately transferred onto the shared drive on an NHS desktop computer before being deleted from the USB stick. Personal details on the programmer will then be re-entered. This process takes approximately 1-2 minutes. The SPN-coded .pdd file will then be send via secure end-to-end encrypted email to the technical team at the Medtronic Bakken Research Centre, Maastricht for processing. This SPN-coded data file is returned (following re: encryption) via secure email to the PI in an .xml file.

Self-report questionnaire (paper format)

Each participant will complete a study participant questionnaire (SPQ), a Medical Outcomes Study Questionnaire Short Form 36 Health Survey (SF-36) (45), and a Rapid Assessment of Physical Activity (RAPA) form (46). Participants will be asked to fill in the questionnaire whilst attending clinic and handed back to the researcher. We will allow a 2-week window period for participants to fill in the questionnaire in any circumstances where a participant is unable to do so in clinic (for example, running late for transport). Pre-paid envelopes to return the forms within this 2-week window will be provided. If the participant cannot perform this task independently, then the researcher will assist the completion of the questionnaire.

Physical frailty assessment

Frailty assessments will be based on the Fried phenotypic criteria as described above (24). Assessments will be performed by the researcher in a clinical room (except gait speed which will be measured in the corridor). See *Table 2* below.

Table 2: Frailty domains and criteria

Characteristic	**Measure**	**Assessment**	**Interpretation**
Weight loss	Weight, BMI (body mass index)	1. Single question: have you lost more than ….kg (10% body weight) in the last 4 years? 2. Height (cm) 3. Weight (kg)	One point in case of either: 1. Positive response to single question 2. BMI < 18.5 kg/m^2 (47)
Muscle weakness	Grip strength (48, 49)	Jamar J00105 hydraulic hand dynamometer Southampton protocol (49)	One point if 'low' Cut-offs stratified by gender and BMI:

			Men BMI ≤ 24: ≤ 29kg BMI 24.1–26: ≤30kg BMI 26.1–28: ≤30kg BMI ≥ 28: ≤32kg Women BMI ≤ 23: ≤17kg BMI 23.1–26: ≤17.3kg BMI 26.1–29: ≤18kg BMI ≥ 29: ≤21kg
Exhaustion	Self-reported	2 questions derived from CES-D questionnaire (50) - How often in the past week did you feel like everything you did was an effort? - How often in the past week did you feel like you could not get going? Responses: - Often [i.e., ≥3 days] - Not often [i.e., 0–2 days]	One point in case of 'often' response to either question
Slow gait speed	Gait speed (50-52)	Participant asked to walk 5 metres (m) at normal walking speed. See below for further detail. .	One point if gait speed <0.6m/s, or unable to perform task. Also subcategories into: Slow: <0.8 m/s (>6s) Very slow: <0.65 m/s (>7.7 s) Extremely slow: <0.50 m/s (>10 s)
Low PA level	Self-reported PA	The Rapid Assessment of Physical Activity (RAPA) questionnaire (53)	One point if RAPA 1 Aerobic score <6

Interpretation of results:

- >/= 3 criteria: frailty

- 1-2 criteria: 'pre- frail'
- 0 criteria: no frailty

Height will be measured using a standard height measure. Weight will be measured using a set of standing scales. Grip strength will be measured using a JAMAR hand hydraulic dynamometer supervised by the researcher following the Southampton protocol (49) (see *Appendix 1*). Exhaustion will be assessed using 2 questions derived from CES-D questionnaire as per the Fried criteria used in the validation study (24) These will be asked verbally. For gait speed, the participant will be asked to walk at a normal pace in the corridor. A start line and finish line will be marked on the corridor wall, alongside a smaller marker 1m on either side. The participant will start 1m before start line, and will stop 1m after the finish line. The researcher will start the stopwatch as soon as the participant's foot crosses the start line and stop recording when the participant's second foot crosses the finish line. Three repetitions will be performed and the mean result used (52). The RAPA questionnaire was chosen to record self-reported PA as it is short, intuitive to use and well validated (53).

Hospital electronic medical records

Accessed by researcher on designated NHS computers.

NEHA Episodes: DARS

A request will be made to DARS (data access request service, NHS Digital) for access to NHS Digital Hospital Episode Statistics (HES) data for each participant in the preceding 12 months. HES data will be requested twice during the study – at 6 months, and 18 months (a fee is associated with each request). HES data includes:

- Emergency department (ED) attendances
    - Date
    - Discharge destination
    - Main diagnostic codes from attendance
- Non-elective hospitalisation episodes
    - Date of admission
    - Date of discharge
    - Discharge destination
    - Main diagnostic codes from admission

- Discharge destination

Rationale for data collection process

Involvement of third party (Medtronic technical team)

Conversion of the CIED download file from .pdd to .xml format can only be done by Medtronic staff using internal software. Only pseudo-anonymised files will be shared with Medtronic. Please see data management plan (DMP) for further detail.

Use of USB stick

Transfer of data from the CIED processor to a computer can only be done using a portable USB stick. Please see DMP for further clarification on data security.

Use of Southampton protocol for hand grip strength

The Southampton protocol for measuring handgrip strength is well established and has been used widely in large epidemiological studies involving older people. It is recommended by the European Working Party on Sarcopenia in Older People (49).

Use of HES data

MFT is a tertiary centre for Cardiology, therefore the local hospital for many device patients may be elsewhere within Greater Manchester. In order to ensure no NEHAs are missed, it is necessary to collect this data from NHS Digital, which monitors all hospital attendances on a national level.

Summary of data to be collected

Personal data (*hospital* records, self-report questionnaire)

1. Age (hospital records, verbally confirmed with patient)
2. Sex (self-report questionnaire)
3. Ethnicity (self-report questionnaire)
4. Postcode (hospital records)
    4.1. Index of deprivation measure
5. Type of accommodation (self-report questionnaire)
6. Living circumstances (self-report questionnaire)
7. Mobility aids (self-report questionnaire)
8. Care provision (self-report questionnaire)

Events/changes in care needs in preceding 12 months

9. Falls (self-report questionnaire)
10. Use of rehabilitation facilities in preceding 12 months (self-report questionnaire)
11. Frequency of use of primary care services (self-report questionnaire)
12. NEHA Episodes (HES)
    12.1. A&E attendances
        12.1.1. Date
        12.1.2. Discharge destination
        12.1.3. Main diagnostic codes from attendance
13. Non-elective hospitalisation episodes
        13.1.1. Date of admission
        13.1.2. Date of discharge
        13.1.3. Discharge destination
        13.1.4. Main diagnostic codes from admission
        13.1.5. Discharge destination

Functional data (self-report questionnaire) (46)

14. Assistance required with activities of daily living (ADLs)

14.1. Dressing

14.2. Walking across a room

14.3. Bathing or showering

14.4. Eating

14.5. Getting out of bed

14.6. Using the toilet

15. Assistance required with instrumental activities of daily living (IADLs)

15.1. Using a map

15.2. Preparing a hot meal

15.3. Shopping for groceries

15.4. Making phone calls

15.5. Taking medications

15.6. Doing work around the house

15.7. Managing money

Medical data

16. Multi-morbidity (hospital records, self-report questionnaire)

16.1. Presence of the long term conditions (LTC) as listed in *Table 3* (54)

17. Presence of multi-morbidity (2+ LTCs)

18. Anti-arrhythmic medication (hospital records)

Cardiac data

19. Most recent left ventricular ejection fraction, systolic and diastolic function (echo parameter) (hospital records)

20. NYHA HF score (I - IV)(55), (self-report questionnaire)

21. AF/pAF/no AF (CIED download)

Device data, (Cardex, CIED download)

22. Type of device

23. Date of insertion

24. Indication for insertion
25. Pacing settings

CIED physiological data, (CIED download)

26. Heart failure risk status (low, medium, high), on day of download
27. OptiVol fluid index, daily
28. Patient activity, daily
29. Average night heart rate, daily
30. Heart rate variability (HRV), daily (note NOT computed if atrial paced >80% of time
31. % Pacing/day, daily
    31.1. Atrial, ventricular
32. Hours a day in AF, daily

Frailty (physical assessment, self-report questionnaire)

33. Physical frailty assessment – Fried criteria (24)

Self-reported PA

34. RAPA score (aerobic, strength and flexibility) (53)

Quality of life

35. Medical Outcomes Study Questionnaire Short Form 36 Health Survey (45)

Table 3: Long term conditions

Long Term Condition	Definition for study
Hypertension	• Self-report • Coded on electronic medical records
Hyperlipidaemia	• Self-report

	• Coded on electronic medical records • non HDL-cholesterol concentration >7.5mmol/L
Ischemic heart disease	• Self-report • Coded on electronic medical records • Previous myocardial infarction, coronary stent, or coronary artery bypass graft
Diabetes (type 1, type 2)	• Self-report • Coded on electronic medical records • HbA1c >48mmol/mol
Arthritis (osteoarthritis, inflammatory arthritis)	• Self-report • Coded on electronic medical records
Heart failure (left ventricular failure, heart failure with preserved ejection fraction)	• Self-report • Coded on electronic medical records • Echo demonstrating ejection fraction <40%
Depression	• Self-report • Coded on electronic medical records
Chronic kidney disease	• Self-report • Coded on electronic medical records • eGFR (estimated glomerular filtration rate) <60%
Osteoporosis	• Self-report • Coded on electronic medical records • T score < -2.5 on DEXA scan
Dementia (plus subtype if available)	• Self-report • Coded on electronic medical records
Chronic obstructive pulmonary disease	• Self-report • Coded on electronic medical records
Atrial fibrillation (permanent, paroxysmal)	• Self-report • Coded on electronic medical records • Device download data
Cancer (excluding skin squamous/basal cell carcinomas)	• Self-report • Coded on electronic medical records
Asthma	• Self-report • Coded on electronic medical records
Stroke/TIA	• Self-report • Coded on electronic medical records

	• Brain imaging demonstrating previous ischaemic or haemorrhagic event

Withdrawal from Study

All participant derived data will be collected on the day of consent, bar the occasional case where a participant wishes to take the questionnaire home and post in back at a later date. Given the short period of time each participant will be actively enrolled in the study, it is highly unlikely a withdrawal of consent will occur. In the event of withdrawal of consent, a consent withdrawal form will be used to document this event. All data collected up to the date of consent withdrawal will be retained, but no further outstanding data collected. This will be made clear in the study information and consent form.

Statistical Analysis

Basic variables from CIED data

CIED data will be processed to create a new set of basic variables for analysis.

1. Mean daily physical activity (MDPA) – mean PA across dataset
2. PA intra-individual variability – as measured by:
    - Range
    - Interquartile range
    - Mean absolute deviation
3. PA surrounding NEHAs – multiple measures.

DOEDA = date of emergency department attendance; DOA = date of hospital admission; DOD = date of discharge; LOS = length of stay (DOD-DOA)

- Difference in PA from MDPA on DOEDA/DOA day -1, day -2, day-3, day-7, day -14
- Difference in PA from MDPA on DOEDA/DOD day +1, day +2, day+3, day+7, day +14
- 'Time till PA recovery' – time from DOEDA/DOD to day regained ≥ MDPA

Descriptive analyses

All data will be stored and analysed using SPSS and 'R' statistical computing software. Basic descriptive statistics will be used to compare different sub-groups of participant (e.g. frail v non-frail). MDPA will be used to facilitate basic comparative analysis using a continuous variable. Determinants of MDPA will be calculated using univariate and multivariable analysis.

PA patterns

As demonstrated in *Figure 3* below, common activity patterns embedded within CIED PA data will be identified using clustering algorithms. Using these identified subtypes of PA as exposures in a longitudinal model with outcome NEHA, multilevel/hierarchical modelling methods (both classical and Bayesian approaches) will be utilised to investigate associations with outcome.

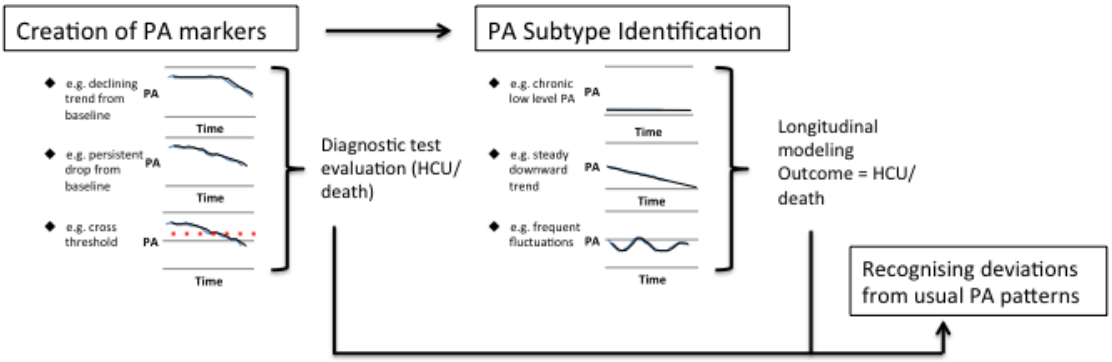

Figure 3

PA and major health events

For this study, major heath events are defined as NEHA episodes. Daily PA in the days leading up to NEHA episodes will be compared to a participant's MDPA, in order to define across the cohort when any observable change in PA is detected by this method. To explore trends in PA preceding NEHA episodes, a nested case control study will be constructed within the dataset, comparing trends in PA preceding NEHA episodes with general trends in PA before index times with no NEHA episodes. This will allow the creation of various 'PA markers' for diagnostic test evaluation methods (sensitivity/specificity, positive and negative predictive value). These PA markers will then be investigated to ascertain if they predict PA subtypes i.e. long-term behaviour patterns. We will also look at how these 'markers' superimposed on identified subtypes can be used to potentially personalise alert systems.

In a similar fashion, we will also explore PA trends following NEHA episodes. There is very little published data on 'recovery time' following hospitalisation episodes in an older population. This study is not powered to investigate this as a primary outcome, however we will measure 'time till PA recovery' following NEHA subtypes (A&E attendance and non-elective hospitalisation episodes), and examine determinants of this.

Risks to Study

Recruitment

A snapshot 'screening' audit using Cardex data in October 2016 found 341 potentially eligible patients on CIED annual follow-up at Manchester Royal Infirmary, an additional 150-250 patients at Wythenshawe are anticipated to be eligible. Recruitment will be undertaken by the PI. An 18-month period has been allocated for initial recruitment. Based on observational studies in similar population, we anticipate a take-up rate of from screening of between 60-80% (56).

Efforts made to maximise recruitment:

- Rigorous screening process
- Recruitment from existing clinical visits
- Low burden of assessment

In the event of lower than anticipated take-up, the recruitment window could be extended beyond 18 months to reach required sample size.

Missing data

This is always a risk during any clinical study. Missing clinical data from electronic health records is expected. Missing data from device downloads is anticipated to be minimal. Self-report questionnaires have been designed to be as short as possible, with clear questions and minimal need for free-text. Questionnaires have been reviewed by the Manchester Academic Health Science Centre Public Patient Involvement panel (MAHSC PPI) to identify any misleading or unclear questions.

Data Management Plan

Description of the data

Directly acquired participant data will be quantitative, generated from; consent forms, questionnaires, physical frailty assessments, CIED downloads and electronic health records. Data from linked electronic health records will be ascertained through NHS Digital Hospital Episode Statistics. Collection and storage of personal, identifiable data will be kept to a minimum, using SPNs wherever possible.

Data collection / generation

All CtC forms returned to the research team by post will be stored in the site file(s). The screening and enrolment log will also be stored in paper format in the site file(s). Three paper copies of the signed consent forms will be produced – one for the participant to keep, one to be placed in the patient's hospital care file, and one to be retained by the study team in the site file(s). A paper case report form (CRF) will be created for each participant. This will be used by the researcher to record data collected during the physical frailty assessment and hospital electronic records. All participant questionnaires are in paper format.

Raw CIED data will be collected via a wireless receiver. See 'data collection processes above for further detail. The process of obtaining data from cardiac devices has been rigorously tested previously, and used as standard in clinical and research practice. This raw data will then be de-identified into SPN-coded format by the PI, before being transferred via secure end-to-end encrypted email to the technical team at the Medtronic Bakken Research Centre, Maastricht for processing. This SPN-coded data file is returned in the same fashion to the PI in an .xml file.

Linked HES data will be collected from NHS Digital via the Data Access Request Service (DARS) service. The NHS numbers of all participants (ascertained from health records) will be shared with the DARS service (via secure online portal), and linked HES data (with corresponding NHS number) will be returned to the PI via the portal. NHS Digital uses NHS standardised coded systems.

Data management, documentation and curation

See *Figure 3* below for an overview of the flow of data through the study.

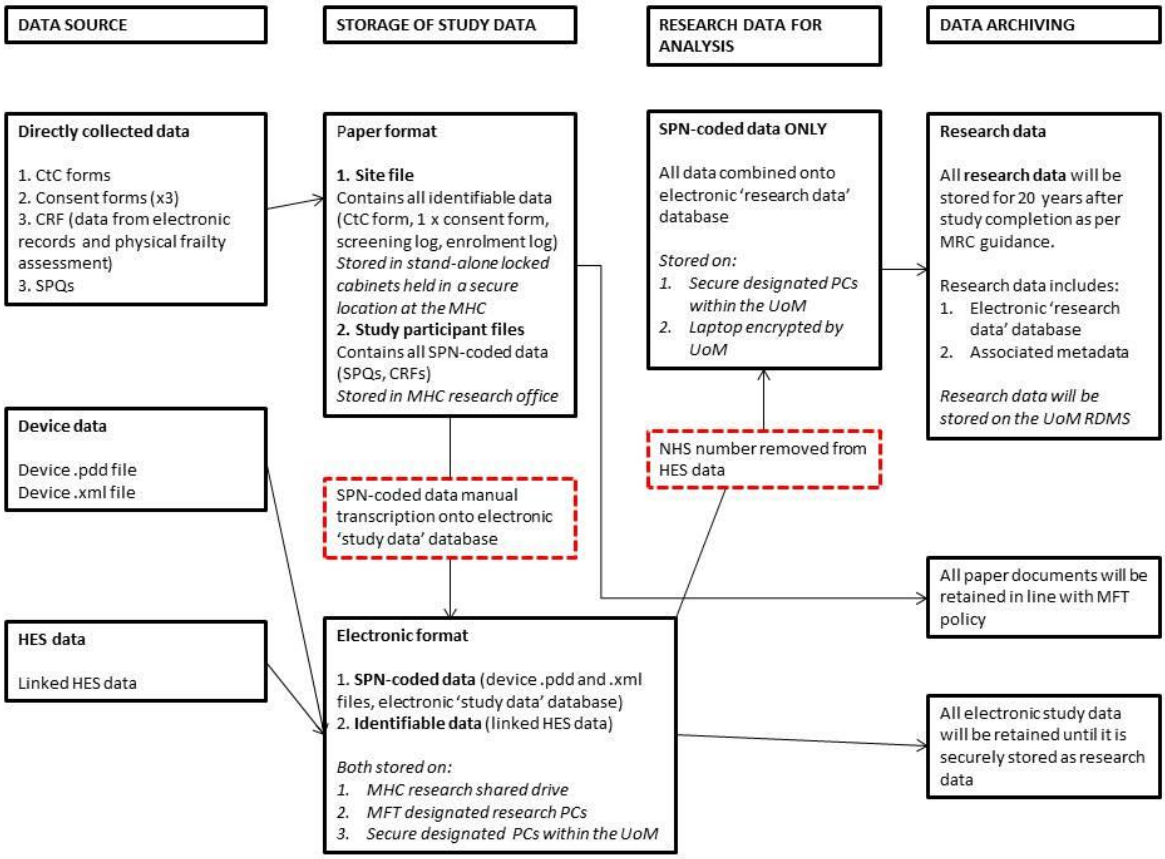

Figure 3

Identifiable data will be collected on:

1. Consent to contact (CtC) forms
2. Consent forms
3. Screening log
4. Enrolment log
5. Linked HES data file

All other documents will be tagged with the SPN only.

One copy of the consent forms, the screening log, and the enrolment log are kept in the site file. The enrolment log will be used as a reference for linking identifiable data with SPNs. The completed SPQs and CRFs will be stored in the study participant files. Data from the SPQs and CRFs will be manually transcribed onto the electronic 'study data' database. Identifiable electronic data (linked HES data) will be stored in three secure locations: MHC research shared drive, an MFT designated research PC, and a designated research PC within the UoM.

All study data in paper format will be stored at the MFT. We have restricted the physical movement of data from the hospital site to the UoM as this is not required for data access by relevant staff – therefore would add an unnecessary complication. As per standard MHC research policy, the site file will be stored in stand-alone locked cabinets held in a secure location at the MFT. Study participant files will be stored in the locked MHC research office.

A single combined 'research data' database will be used for analysis (SPN-coded data only). In addition to allocated UoM PCs, this database will also be stored on a designated laptop will be encrypted by the UoM IT team. Metadata will be produced regarding data collection, management and analysis, in order for any secondary users to understand the data.

The study has been registered with the UoM Research Data Management Service (RDMS), where all electronic research data and associated metadata will be stored. This is an internal platform facilitation the storage, management, preservation, publication and sharing of research data.

Data security and confidentiality

UoM and MFT policies assure information security in line with recognised standards, and support compliance with relevant legislation. Personal data relating to the study will be stored securely in either paper or electronic format as laid out in *Figure 3*. All paper copies of study materials will be stored in either the site file(s) or study participant files. The site file(s) contain identifiable data, and will be kept on-site at the MFT in designated secure, stand-alone cabinets held in a secure location in the MHC. Study participant files contain all paper format SPN-coded data and will be stored in the MHC research office. The MHC research office is located in a 'staff-only' section of the hospital and is locked/occupied by research staff at all times. All identifiable study data in electronic format will be encrypted and backed-up, stored on secure designated locations only. Access to identifiable data will granted to the PI, any additional research staff delegated to the PATTErn study, supervisory team and members of the clinical care team (in any case of clinical need). Authorised representatives from the UoM, NHS or regulatory bodies may be granted access to personal data for audit and monitoring purposes. All staff accessing study data will sign the delegation log in the HRA statement of activities file stored at the MHC research office. As per MFT/UoM policy, all members of staff with access to study material are fully trained in research ethics and IT security, bound to professional standards and accredited with up to date NIHR Good Clinical Practice (GCP) training.

The USB stick used to transfer CIED download .pdd files from the processor onto the trust PCs will be encrypted by MFT IT services. Once data has been safely transferred onto the PC, the USB stick will be wiped clean. The USB stick will remain on site in the MHC at all times.

A pseudo-anonymised, SPN-coded 'research data' database will be created for all analysis and only this data will be used and shared out with the study team as per the terms laid out in ethical guidelines, and consent forms. Due to the nature of the data collected, it is not feasible to create a fully anonymised database. Whist re-identification will not be possible directly from the database, indirectly this may be possible if a person also has access to other confidential healthcare databases (for example, electronic patient records). This data will be stored on designated MFT and UoM computers.

PCs within the MFT and UoM have been identified for storing and processing the research data. Once the PC has loaded the operating system a local, password protected computer account is required to login to the PC. This account is unique to the primary user of the computer and only the account owner knows the password. Identified PCs have Windows firewall enabled and configured to prevent remote access. The PCs have been configured to automatically update their antivirus signatures daily and have been configured to download and install any Microsoft operating system and application security patches automatically from the Microsoft update service. The secure MFT and UoM servers will be used to store and back-up all electronic data daily.

In addition, a UoM encrypted laptop will be allocated to store SPN-coded research data and associated metadata only for the duration of the study. This will allow the PI to work with the data as part of her MD out with the trust/university sites. The PI will take full responsibility for the security of the laptop and follow UoM IT security protocols at all times.

Data archiving, sharing and access

All electronic research data and associated metadata will be stored with the UoM RDMS. Research data will be made available for other researchers and the public after results have been validated, presented, and published in peer-reviewed journals. Where we engage with commercial or other collaborators, and where appropriate, we reserve the right to share the data and analysis under Non-Disclosure Agreement.

Published data will be available through the UoM Current Research Information System. As per UoM policy, all peer-reviewed journal articles and conference papers will be open access, and accessible

via the Open Access Gateway. All Published outputs will be assigned a Digital Object Identifier to reference the data in publications.

Electronic study data will be retained until all study data is collected, processed and stored securely as research data (no longer than 24 months from start of study, see *Figure 1*). All paper documents will be retained in line with MFT policy. The consent form which is filed in the patient notes will be stored there indefinitely. All research data will be retained on the UoM RDMS, in possession of the UoM for a minimum of 20 years.

Responsibilities

The PI will take day-to-day responsibility for the quality of the data acquired, the datasets, and transfer for storage with the RDMS. Overall responsibility for the data will lie with the PI's primary academic supervisor at the UoM.

Dissemination of Results and Publication Policy

Results of this study will be disseminated to the academic community by publication in peer reviewed scientific journals, conference presentation and presentations at local academic meetings. Results will be disseminated to participants by letter, which will provide a summary of findings, and links to further information. We will also hold an event for participants and the public to explain the results of the study, for example through MICRA (Manchester Institute for Collaborative Research on Ageing) public event meetings. The wider public will be informed of findings through UoM media channels.

Project Management

This study will be co-ordinated by the PI. Study sponsor is the University of Manchester. Study development and delivery is supported by the Research and Innovation Division at Manchester University NHS Foundation Trust (Dr Iain McLean PhD Senior Divisional Research Manager).

Ethics

Ethical approval is mandatory for this study to commence. This shall be sought on confirmation of funding via the Integrated Research Application System (IRAS). This is a minimal risk observational study. Data collection at recruitment and follow-up has been scheduled to cause minimal inconvenience to patients and will coincide with appointments that constitute standard clinical care. The PI and all members of the research team are trained in assessing capacity to consent in clinical research.

Funding and Resources

PI (JKT) salary and data access costs will be funded by Medtronic. Study administrative costs will be met by research funds at the MFT. The project has been designed to be cost neutral to the host NHS trust.

References

1. National Service Framework for Older People, Department of Health for England, 2001.

2. Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. The Lancet. 2013;381(9868):752-62.

3. Gill TM, Baker DI, Gottschalk M, Peduzzi PN, Allore H, Byers A. A program to prevent functional decline in physically frail, elderly persons who live at home. New England Journal of Medicine. 2002;347(14):1068-74.

4. Beswick AD, Rees K, Dieppe P, Ayis S, Gooberman-Hill R, Horwood J, et al. Complex interventions to improve physical function and maintain independent living in elderly people: a systematic review and meta-analysis. The Lancet. 2008;371(9614):725-35.

5. Gillespie LD, Gillespie WJ, Robertson MC, Lamb SE, Cumming RG, Rowe BH. Interventions for preventing falls in elderly people. Cochrane Database Syst Rev. 2003;4.

6. Stuck AE, Egger M, Hammer A, Minder CE, Beck JC. Home visits to prevent nursing home admission and functional decline in elderly people: systematic review and meta-regression analysis. Jama. 2002;287(8):1022-8.

7. Lewis G. Predicting who will need costly care. How best to target preventative health, housing and social programmes. The Kings Fund 2007. Available at URL: http://www.kingsfund.org.uk/sites/files/kf/Predicting book final.pdf.

8. Purdy S. Avoiding hospital admissions. What does the research evidence say?. The King's Fund 2010.

9. Hutt R, Rosen R, McCauley J. Case managing long-term conditions: what impact does it have in the treatment of long-term conditions. London: Kings Fund. 2004.

10. Chiu WK, Newcomer R. A Systematic Review of Nurse-Assisted Case Management to Improve Hospital Discharge Transition Outcomes for the Elderly. Professional case management. 2007;12(6):330-6.

11. Oeseburg B, Wynia K, Middel B, Reijneveld SA. Effects of case management for frail older people or those with chronic illness: a systematic review. Nursing research. 2009;58(3):201-10.

12. Gonseth J, Guallar-Castillón P, Banegas JR, Rodríguez-Artalejo F. The effectiveness of disease management programmes in reducing hospital re-admission in older patients with heart failure: a systematic review and meta-analysis of published reports. European heart journal. 2004;25(18):1570-95.

13. McAlister FA, Stewart S, Ferrua S, McMurray JJ. Multidisciplinary strategies for the management of heart failure patients at high risk for admission: a systematic review of randomized trials. Journal of the American College of Cardiology. 2004;44(4):810-9.

14. Swindle JP, Rich MW, McCann P, Burroughs TE, Hauptman PJ. Implantable cardiac device procedures in older patients: use and in-hospital outcomes. Archives of Internal Medicine. 2010;170(7):631-7.

15. Kirkfeldt RE, Johansen JB, Nohr EA, Jørgensen OD, Nielsen JC. Complications after cardiac implantable electronic device implantations: an analysis of a complete, nationwide cohort in Denmark. European heart journal. 2013:eht511.

16. Mitchell P, Marle D, Donkor A, Shote, Aminat, McDonagh T, et al. The national heart failure audit April 2013 - March 2014. 2014.

17. Conraads VM, Spruit MA, Braunschweig F, Cowie MR, Tavazzi L, Borggrefe M, et al. Physical Activity, Measured with Implanted Devices, Predicts Patient Outcome in Chronic Heart Failure. Circulation: Heart Failure. 2014:CIRCHEARTFAILURE. 113.000883.

18. Lien CT, Gillespie ND, Struthers AD, McMurdo ME. Heart failure in frail elderly patients: diagnostic difficulties, co-morbidities, polypharmacy and treatment dilemmas. European journal of heart failure. 2002;4(1):91-8.

19. McNallan SM, Singh M, Chamberlain AM, Kane RL, Dunlay SM, Redfield MM, et al. Frailty and healthcare utilization among patients with heart failure in the community. JACC: Heart Failure. 2013;1(2):135-41.

20. Whellan DJ, Ousdigian KT, Al-Khatib SM, Pu W, Sarkar S, Porter CB, et al. Combined heart failure device diagnostics identify patients at higher risk of subsequent heart failure hospitalizations: results from PARTNERS HF (Program to Access and Review Trending Information and Evaluate Correlation to Symptoms in Patients With Heart Failure) study. Journal of the American College of Cardiology. 2010;55(17):1803-10.

21. Cowie MR, Sarkar S, Koehler J, Whellan DJ, Crossley GH, Tang WHW, et al. Development and validation of an integrated diagnostic algorithm derived from parameters monitored in implantable devices for identifying patients at risk for heart failure hospitalization in an ambulatory setting. European heart journal. 2013;34(31):2472-80.

22. Hawkins NM, Virani SA, Sperrin M, Buchan IE, McMurray JJ, Krahn AD. Predicting heart failure decompensation using cardiac implantable electronic devices: a review of practices and challenges. European journal of heart failure. 2015.

23. Manemann SM, Chamberlain AM, Boyd CM, Gerber Y, Dunlay SM, Weston SA, et al. Multimorbidity in heart failure: effect on outcomes. Journal of the American Geriatrics Society. 2016;64(7):1469-74.

24. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, et al. Frailty in older adults evidence for a phenotype. The Journals of Gerontology Series A: Biological Sciences and Medical Sciences. 2001;56(3):M146-M57.

25. Fried LP, Kronmal RA, Newman AB, Bild DE, Mittelmark MB, Polak JF, et al. Risk factors for 5-year mortality in older adults: the Cardiovascular Health Study. Jama. 1998;279(8):585-92.

26. Rockwood K, Mitnitski A. Frailty in relation to the accumulation of deficits. The Journals of Gerontology Series A: Biological Sciences and Medical Sciences. 2007;62(7):722-7.

27. Clegg A, Bates C, Young J, Ryan R, Nichols L, Teale EA, et al. Development and validation of an electronic frailty index using routine primary care electronic health record data. Age and ageing. 2016;45(3):353-60.

28. Rockwood K, Song X, MacKnight C, Bergman H, Hogan DB, McDowell I, et al. A global clinical measure of fitness and frailty in elderly people. Canadian Medical Association Journal. 2005;173(5):489-95.

29. Rolfson DB, Majumdar SR, Tsuyuki RT, Tahir A, Rockwood K. Validity and reliability of the Edmonton Frail Scale. Age and ageing. 2006;35(5):526-9.

30. Bouillon K, Kivimaki M, Hamer M, Sabia S, Fransson EI, Singh-Manoux A, et al. Measures of frailty in population-based studies: an overview. BMC geriatrics. 2013;13(1):64.

31. Murphy SL. Review of physical activity measurement using accelerometers in older adults: considerations for research design and conduct. Preventive medicine. 2009;48(2):108-14.

32. Yang C-C, Hsu Y-L. A review of accelerometry-based wearable motion detectors for physical activity monitoring. Sensors. 2010;10(8):7772-88.

33. Van Remoortel H, Giavedoni S, Raste Y, Burtin C, Louvaris Z, Gimeno-Santos E, et al. Validity of activity monitors in health and chronic disease: a systematic review. International Journal of Behavioral Nutrition and Physical Activity. 2012;9(1):1.

34. Trost SG, McIver KL, Pate RR. Conducting accelerometer-based activity assessments in field-based research. Medicine and science in sports and exercise. 2005;37(11):S531.

35. Taraldsen K, Askim T, Sletvold O, Einarsen EK, Bjåstad KG, Indredavik B, et al. Evaluation of a body-worn sensor system to measure physical activity in older people with impaired function. Physical therapy. 2011;91(2):277-85.

36. Pressler A, Danner M, Esefeld K, Haller B, Scherr J, Schömig A, et al. Validity of cardiac implantable electronic devices in assessing daily physical activity. International journal of cardiology. 2013;168(2):1127-30.

37. (NICE) NIFHACE. NICE. Implantable cardioverter defibrillators and cardiac resynchronisation therapy for arrhythmias and heart failure. Technology appraisal guidance [TA314]. 25 June 2014.

38. Abraham WT, Fisher WG, Smith AL, Delurgio DB, Leon AR, Loh E, et al. Cardiac resynchronization in chronic heart failure. New England Journal of Medicine. 2002;346(24):1845-53.

39. Cleland JG, Daubert J-C, Erdmann E, Freemantle N, Gras D, Kappenberger L, et al. The effect of cardiac resynchronization on morbidity and mortality in heart failure. New England Journal of Medicine. 2005;352(15):1539-49.

40. Kawabata M, Fantoni C, Regoli F, Raffa S, Pastori F, Fratini S, et al. Activity monitoring in heart failure patients with cardiac resynchronization therapy. Circulation Journal. 2007;71(12):1885-92.

41. Boxer R, Kleppinger A, Ahmad A, Annis K, Hager D, Kenny A. The 6-minute walk is associated with frailty and predicts mortality in older adults with heart failure. Congestive Heart Failure. 2010;16(5):208-13.

42. Gottdiener JS, Arnold AM, Aurigemma GP, Polak JF, Tracy RP, Kitzman DW, et al. Predictors of congestive heart failure in the elderly: the Cardiovascular Health Study. Journal of the American College of Cardiology. 2000;35(6):1628-37.

43. Lakatta EG. So! What's aging? Is cardiovascular aging a disease? Journal of molecular and cellular cardiology. 2015;83:1-13.

44. Conraads VM, Tavazzi L, Santini M, Oliva F, Gerritse B, Yu C-M, et al. Sensitivity and positive predictive value of implantable intrathoracic impedance monitoring as a predictor of heart failure hospitalizations: the SENSE-HF trial. European heart journal. 2011:ehr050.

45. McHorney CA, Ware Jr JE, Lu JR, Sherbourne CD. The MOS 36-item Short-Form Health Survey (SF-36): III. Tests of data quality, scaling assumptions, and reliability across diverse patient groups. Medical care. 1994:40-66.

46. Gale CR, Cooper C, Sayer AA. Prevalence of frailty and disability: findings from the English Longitudinal Study of Ageing. Age and ageing. 2015;44(1):162-5.

47. Liljas AE, Carvalho LA, Papachristou E, Oliveira CD, Wannamethee SG, Ramsay SE, et al. Self-Reported Hearing Impairment and Incident Frailty in English Community-Dwelling Older Adults: A 4-Year Follow-Up Study. Journal of the American Geriatrics Society. 2017;65(5):958-65.

48. Lauretani F, Russo CR, Bandinelli S, Bartali B, Cavazzini C, Di Iorio A, et al. Age-associated changes in skeletal muscles and their effect on mobility: an operational diagnosis of sarcopenia. Journal of applied physiology. 2003;95(5):1851-60.

49. Roberts HC, Denison HJ, Martin HJ, Patel HP, Syddall H, Cooper C, et al. A review of the measurement of grip strength in clinical and epidemiological studies: towards a standardised approach. Age and Ageing. 2011;40(4):423-9.

50. Afilalo J, Alexander KP, Mack MJ, Maurer MS, Green P, Allen LA, et al. Frailty assessment in the cardiovascular care of older adults. Journal of the American College of Cardiology. 2014;63(8):747-62.

51. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, Boirie Y, Cederholm T, Landi F, et al. Sarcopenia: European consensus on definition and diagnosis Report of the European Working Group on Sarcopenia in Older People. Age and ageing. 2010:afq034.

52. Lusardi MM, Pellecchia GL, Schulman M. Functional performance in community living older adults. Journal of Geriatric Physical Therapy. 2003;26:14-22.

53. Topolski TD, LoGerfo J, Patrick DL, Williams B, Walwick J, Patrick MMB. Peer reviewed: the Rapid Assessment of Physical Activity (RAPA) among older adults. Preventing chronic disease. 2006;3(4).

54. Salive ME. Multimorbidity in older adults. Epidemiologic reviews. 2013:mxs009.

55. Dolgin M, Association CCNYH. Nomenclature and criteria for diagnosis of diseases of the heart and great vessels: the Criteria Committee of the New York Heart Association: Little, Brown; 1994.

56. Lee DS, Austin PC, Rouleau JL, Liu PP, Naimark D, Tu JV. Predicting mortality among patients hospitalized for heart failure: derivation and validation of a clinical model. Jama. 2003;290(19):2581-7.