Study Title: Feasibility study of the use of point-of-care NP measurement in primary care in patients with heart failure

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There are no conflicts of interest to declare.

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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1. SYNOPSIS

Study Title	Feasibility study of the use of point-of-care NP measurement in primary care in patients with heart failure	
Study Design	Feasibility study	
Study Participants	Adult patients (>18y) diagnosed with heart failure, including both heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF), in 2-3 GP practices.	
Planned Sample Size	30 patients + 16 HCPs	
Planned Study Period	15 months (3 months recruitment + 12 months follow-up)	
	Objectives	**Outcome Measures**
Primary	Variability in NP measured by POC NP in primary care	Between-person variability of POC NP Within-person variability of POC NP
Secondary	Feasibility of POC NP in primary care	Proportion of planned tests for which results are available.
	Potential for impact on primary care decision-making	Proportion of NP tests that GPs report would have changed or did change decision-making process
	Compliance with NP measurement regime	Proportion of proposed tests actually carried out
	Willingness to participate in long term cohort studies of POC NP	Likert scores for patient acceptability Likert scores for nurse and GP acceptability Patient views about POC NP testing in primary care Nurse and GP views about POC NP testing in primary care Recruitment rate Retention rate
	Device and operator performance	Comparison to lab NT-proBNP measures EQA comparison EQA precision assessment

2. ABBREVIATIONS

AF	Atrial Fibrillation

BP	Blood Pressure
CI	Chief Investigator
CRF	Case Report Form
CTRG	Clinical Trials & Research Governance, University of Oxford
EQA	External Quality Assessment
GCP	Good Clinical Practice
GP	General Practitioner
HCP	Health Care Professional
HF	Heart Failure
HFpEF	Heart Failure with preserved Ejection Fraction
HFrEF	Heart Failure with reduced Ejection Fraction
ICF	Informed Consent Form
LVEF	Left Ventricular Ejection Fraction
LVF	Left Ventricular Failure
NHS	National Health Service
NP	Natriuretic Peptide
NRES	National Research Ethics Service
NT-proBNP	N-terminal prohormone of B-type Natriuretic Protein
NYHA	New York Heart Association
PI	Principal Investigator
PIL	Participant/ Patient Information Leaflet
POC	Point of Care
R&D	NHS Trust R&D Department
REC	Research Ethics Committee
SOP	Standard Operating Procedure

3. BACKGROUND AND RATIONALE

Heart failure (HF) is a chronic disease, which can result in significant morbidity and mortality. Natriuretic peptide (NP) levels, have been shown to correlate with poor prognosis in heart failure, [National Clinical Guideline Centre 2010] and it has been postulated that routine monitoring of NP could assist in improving care of heart failure patients in the community. [National Clinical Guideline Centre 2010] Much of the care for patients with heart failure occurs in the community, either in primary care, or through specialist community heart failure nurses, with referral to secondary care in the event of acute illness or deterioration. Recent advances in technology provide the possibility of point-of-care NP testing, but there is currently no evidence to support the use of such devices as part of routine care of heart failure patients in primary care.

The primary aim of this study is to determine the variability in NP measurements made using point-of-care (POC) NP technology in heart failure patients in primary care settings, including both between- and within-person variability.

Secondary aims include the feasibility and acceptability of routine NP monitoring for heart failure patients in primary care; the potential for impact on primary care decision-making; and device and operator performance. If the technology is proved to be feasible and acceptable, then further research to assess the clinical benefit of NP monitoring would be appropriate.

The intervention in this study is point-of-care NT-proBNP measurement, using the Roche cobas h 232 device, added to current clinical measures at all visits. As this is a feasibility study, there is no control group.

Both BNP and NT-proBNP appear to have similar predictive value in heart failure [National Clinical Guideline Centre 2010, Denny 2011]. However, NT-proBNP appears to have less biological variation than BNP in HF patients [Bruins 2004, Frankenstein 2009, Meijers 2017, Nordenskjold 2013, Schindler 2016, Takeda 2009]. In the monitoring setting, reduced biological variation is likely to be beneficial; so we have chosen to use NT-proBNP for this study.

A previous horizon scan of POC NP devices suitable for use in the diagnosis of heart failure in primary care identified two POC NT-proBNP devices [Denny 2011]. Of these, the device which we propose to use in this study is the one for which the most evidence is available, and is also the only one for which a UK distributor could be identified. It also carries a CE mark and is currently marketed in the UK as a point-of-care assessment of NT-proBNP for diagnosis of heart failure.

There are very few risks associated with point-of-care NP measurement. As a venous blood sample is required, some participants may experience bruising or bleeding at the site from which the sample is taken, as well as transient pain associated with phlebotomy. This is not considered to be an excessive risk, as heart failure patients typically require frequent blood tests for monitoring of other biochemical markers (e.g. renal function in patients taking ACE inhibitors), and so would already be exposed to these risks. As NP measurement is not currently part of the clinical pathway once heart failure is diagnosed, [National Clinical Guideline Centre 2010] there may be limited benefit to participants from additional measurement of NP. However, clinicians will not be blinded to the results of the POC NP, and so it is possible that changes in NP would be investigated further, which may result in earlier treatment or avoided exacerbation for the patient. However, conversely, there may be a risk of unnecessary further investigation in some patients.

Included patients will have a confirmed diagnosis of heart failure. Patients with both preserved (HFpEF) and reduced (HFrEF) will be eligible for inclusion in the study.

4. OBJECTIVES AND OUTCOME MEASURES

Objectives	**Outcome Measures**	**Timepoint(s) of evaluation of this outcome measure (if applicable)**

Primary Objective Variability in NP measured by POC NP in primary care	Between-person variability of POC NP Within-person variability of POC NP	All visits All visits
Secondary Objectives		
Feasibility of POC NP in primary care	Proportion of planned tests for which results are available.	All visits
Potential for impact on primary care decision-making	Proportion of NP tests that GPs report would have changed or did change decision-making process	All visits
Compliance with NP measurement regime	Proportion of proposed tests actually carried out	All visits
Willingness to participate in long term cohort studies of POC NP	Likert scores for patient acceptability Likert scores for nurse and GP acceptability Patient views about POC NP testing in primary care Nurse and GP views about POC NP testing in primary care Recruitment rate Retention rate	12 month visit Start and end of clinician involvement. Focus groups following 12 month visit Focus groups after end of clinician involvement Baseline visit / approach 6 and 12 month visits
Device and operator performance	Comparison to lab NT-proBNP measures EQA comparison EQA precision assessment	Baseline, 6 and 12 month visits Convenient time for clinical staff Convenient time for clinical staff

5. STUDY DESIGN

This is an observational feasibility study, in which the intervention (POC NP) will be introduced to all participants. Neither clinicians nor participants will be blinded to the presence or the results of the POC NP measurements.

The anticipated length of the study is 15 months. This consists of 3 months recruitment, and 12 months follow-up. Each participant will be followed up for 12 months, with a minimum of 3 visits, at baseline, 6 and 12 months (see flowchart below). However, it is intended that POC NP will also be employed at any additional appointment for heart failure made by a study patient during the 12 month study period.

Data will be collected on paper CRFs. At each visit, a venous blood sample will be taken and used to measure POC NT-proBNP using the Roche cobas h 232 POC device. The NT-proBNP result will be recorded, along with the patient's weight, blood pressure, and pulse. An additional venous blood sample will be taken to assess the patient's renal function and for lab NT-proBNP measurement. The renal function test is required as increases in NT-proBNP can be due to decreased renal function.

At the baseline, 6 month, and 12 month visits, the patient will also complete a Minnesota Living with HF questionnaire, and the clinician will assess their functional status using the NYHA scoring system. We will also record current medication, and concurrent medical problems at each visit.

At the baseline visit only, in addition to consent, we will collect basic demographic data (age, gender and ethnicity), as well as data on the type of HF (HRpEF or HFrEF), and presence of AF (including paroxysmal or not) or other arrhythmias.

At the 12-month visit, patients will be asked to complete a Likert score of the acceptability of POC NP, and will be invited to a focus group to discuss their experience of routine POC NP testing in primary care. There will also be notes review to identify dates of any hospital admissions and reason for admission, as well as dates and primary reasons for all primary care appointments during the study period.

At additional appointments for heart failure, the reason for the appointment will be recorded.

Following completion of the study, nurses and GPs will also be asked to complete a Likert score of the acceptability of POC NP, and will be invited to take part in focus groups to discuss their experience of routine POC NP testing in primary care.

6. PARTICIPANT IDENTIFICATION

6.1. Study Participants

Adult patients (>18y) diagnosed with heart failure (HFrEF or HRpEF) by cardiologist and/or echocardiography, and managed in primary care. Participants may include both newly diagnosed and existing patients.

6.2. Inclusion Criteria

- Participant is willing and able to give informed consent for participation in the study.
- Male or female, aged 18 years or above.
- Confirmed diagnosis of heart failure made by cardiologist and/or echocardiography

- Currently managed in a primary care setting where the clinician is willing to take part in routine POC NP monitoring.

6.3. Exclusion Criteria

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

- Participant is considered to be terminally ill or receiving palliative care for another condition only at the time of recruitment

7. STUDY PROCEDURES

See Appendix B for a schedule of study procedures in tabular form.

7.1. Recruitment

Potential participants meeting the inclusion criteria will be identified from the electronic records or patient lists of GP practices taking part in the study. Suitability for inclusion in the study will be assessed by a GP or nurse practitioner against the criteria in section 6 above.

Identified patients will be invited to take part in the study by letter (Appendix C1), with an enclosed Participant Information Leaflet (Appendix C2). A log will be kept of all invited patients, and patients will only be invited to take part by letter once.

Invited patients who attend for a routine heart failure appointment with a member of the study team (GP or practice nurse) will be approached to take part in the study. A log will be kept, so that patients will not be approached to take part in the study more than once.

7.2. Informed Consent

Participants who are approached to take part in the study will be presented with written and verbal versions of the Participant Information Leaflet (Appendix C2) and Informed Consent Form (Appendix C3), detailing no less than: the exact nature of the study; what it will involve for the participant; the implications and constraints of the protocol; and any risks involved in taking part. It will be clearly stated that the participant is free to withdraw from the study at any time for any reason without prejudice to future care, without affecting their legal rights, and with no obligation to give the reason for withdrawal.

The participant will be allowed as much time as wished to consider the information, and the opportunity to question the Investigator, their GP or other independent parties to decide whether they will participate in the study. 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 will be suitably qualified and experienced, and have been authorised to do so by the Chief/Principal Investigator. A copy of the signed Informed Consent will be given to the participant. A second copy of the form will be retained at the study site, and the original will be returned to the study team at the Nuffield Department of Primary Care Health Sciences.

The participant must personally sign and date the latest approved version of the Informed Consent form before any study specific procedures are performed. Separate consent forms will be used for the main study (Appendix C3) and the qualitative interviews (Appendices C6 and C7).

As recruitment to the study is one of the outcomes, we will keep a record of how many patients have been approached, and whether or not they agreed to take part in the study. This data will not be identifiable, and will not be associated with any patient details. Where a patient chooses not to take part in the study, we will give them the option of articulating why they have chosen not to do so, and we will record this information.

7.3. Baseline Assessments

At the initial visit, in addition to obtaining consent and receiving normal clinical care, the participant will have the following assessments:

- Demographic data collection (age, gender, ethnicity)
- Point of care NT-proBNP measurement
- Additional venous blood samples for lab NT-proBNP and renal function measurements
- Measurement of weight, blood pressure and pulse
- NYHA functional assessment (completed by clinician)
- Minnesota Living with Heart Failure Questionnaire (completed by participant)
- Recording of type of HF patient has been diagnosed with
- Recording of concomitant medication
- Recording of medication changes made at the appointment
- Recording of concurrent medical problems
- Recording of presence of arrhythmias, including AF
- Recording of the qualification level of the person taking the POC NT-proBNP measurement

7.4. Subsequent Visits

Routine appointments for heart failure

Where possible, POC NP will be carried out following all primary care appointments for heart failure made by study participants during the 12-month follow up period. At each of these, in addition to normal routine care, the participant will have the following assessments:

- Point of care NT-proBNP measurement
- Additional venous blood sample for renal function measurement
- Measurement of weight, blood pressure and pulse
- Update of concomitant medication record
- Recording of medication changes made at the appointment
- Update of concurrent medical problems
- Update of presence of arrhythmias, including AF
- Recording of the qualification level of the person taking the POC NT-proBNP measurement
- Recording of reason for appointment

Due to the potential additional waiting time that may be required of the patient to see someone for POC testing, patients will be requested but not required to stay for additional assessments after routine appointments. Where patients choose not to stay, the POC tests will be regarded as planned but not carried out for the purposes of analysis.

6 month visit (5-7 month window)

This will be a clinic visit with a member of the study team. In addition to normal routine care, the participant will have the following assessments:

- Point of care NT-proBNP measurement
- Additional venous blood samples for lab NT-proBNP and renal function measurements
- Measurement of weight, blood pressure and pulse
- NYHA functional assessment (completed by clinician)
- Minnesota Living with Heart Failure Questionnaire (completed by participant)
- Update of concomitant medication record
- Recording of medication changes made at the appointment
- Update of concurrent medical problems record
- Update of record of presence of arrhythmias, including AF
- Recording of the qualification level of the person taking the POC NT-proBNP measurement

12 month visit (11-13 month window)

This will be a clinic visit with a member of the study team. In addition to normal routine care, the participant will have the following assessments:

- Point of care NT-proBNP measurement
- Additional venous blood samples for lab NT-proBNP and renal function measurements
- Measurement of weight, blood pressure and pulse
- NYHA functional assessment (completed by clinician)
- Minnesota Living with Heart Failure Questionnaire (completed by participant)
- Update of concomitant medication record
- Recording of medication changes made at the appointment
- Update of concurrent medical problems record
- Update of record of presence of arrhythmias, including AF
- Recording of the qualification level of the person taking the POC NT-proBNP measurement
- Likert assessment of acceptability of routine POC NP measurement (completed by participant)
- Invitation to take part in focus group

Effect on decision-making process

After each patient visit, the patient's clinician (typically their GP) will be presented with their CRF (in the case of scheduled research visits), or their POC NT-proBNP result (in the case of routine heart failure appointments). Clinicians will be asked as an expert informant if the POC NT-proBNP result would have either changed their decision making process, or not affected their decision making process.

As this is a feasibility study of point-of-care NT-proBNP in primary care, and there is currently no NICE guidance on the use of NT-proBNP for monitoring heart failure, we are not asking clinicians to incorporate either point-of-care or lab NT-proBNP results into their clinical management. However, since they will have access to both results, and it is possible that they will wish do so, or would have done so if they had access at the time of making management decisions, we are collecting data on this. In most cases, we anticipate that clinical decisions will have been made without sight of either point of care or lab NT-proBNP results, and so we will be asking about whether knowledge of the result would have changed management if it was available at the time of decision making. However, we will allow for reporting of instances where results have influenced decision making, or have resulted in changes to management

once they have become available. There will be space for the clinician to add free text to explain their choice if they wish.

Focus groups and assessment of clinician acceptability

Participants will be invited to take part in a focus group at their 12 month visit, and may be contacted by their preferred contact means to remind them of this opportunity after this visit. Clinicians carrying out the POC NP measurement will also be invited to take part in separate focus groups. A separate information leaflet (Appendices C4 & C5) will be provided to potential participants, and a separate consent form (Appendices C6 and C7) will be completed by participants taking part in focus groups. Invitation letters and reply slips may be used where appropriate (Appendices C8-C11.) Focus groups will take place at a mutually convenient time and location, with 3-8 participants and 2 facilitators. They will investigate participants' experiences of point of care NP and will be audio and video recorded. The questions for the focus groups will be formulated with help from the project team including PPI representatives, but the topics for the patient focus groups are likely to include:

- The acceptability of additional blood tests for monitoring
- Their opinions of POC test vs lab test
- The practicality of having blood test done with POC test whenever they see the doctor for heart failure
- Their feelings about being in another study that used this test to help the doctor manage their heart failure
- How they would hope to benefit if the doctor used these tests to manage their heart failure

Topics for the focus groups with clinicians will include:

- The clinical utility of NP measurement in monitoring heart failure
- The technical acceptability of POC device
- The practicality of incorporating POC NP into usual care
- The impact of POC NP on decision making
- Their opinions of POC NP vs lab NP

Assessment of clinician acceptability

All clinicians involved in the study will be asked to complete an assessment of clinician acceptability after the last patient visit at their site. This will include collection of the following data:

- Study site
- Clinician type (nurse, doctor, HCA)
- Likert assessment of acceptability of routine POC NP measurement (completed by clinician)

7.5. Sample Handling

At each study visit and routine heart failure visit, venous blood samples will be taken from participants for POC NP and renal function testing. At study visits (at baseline, 6 and 12 months), an additional venous blood sample will be taken for lab-based NT-proBNP testing.

Heparin tube (green cap) 6.5 ml for renal function tests (eGFR and serum creatinine)

Heparin tube (green cap) 6.5 ml for POC NT-proBNP test (only 150µL is used for the test, but 6.5ml will need to be drawn, as per device instructions.)

Serum separating (SST) tube (yellow cap) 6 ml for lab-based NT-proBNP test (baseline, 6 and 12 month visits only)

Laboratory samples

Lab samples will be processed at an NHS laboratory, with results returned through the normal NHS processes. They will then be available to the patient's clinical team in the same way as any other clinical blood test. The results will be transcribed onto a CRF for research purposes. Once processed, samples will not be stored further.

Sample for POC NP test

150µL of the sample taken for the POC NP test will be applied to the test strip in accordance with the manufacturer's instructions, immediately following sample collection. The result of the POC NP test will be reported by the device approximately 12-14 minutes after sample application, and will be noted on the CRF. The remainder of the POC NP venous sample, and the POC test strip containing the 150µL sample will be disposed of in the clinical waste stream once the POC test result has been recorded.

Use of NP in clinical management within the study

The study is set up so that NP measurements will typically be presented to treating clinicians after the patient appointment. However, as this is an unblinded study, some clinicians many choose to alter their decisions based on either the POC NP result or the laboratory NP result. In the initial clinician training for the study, we will include guidance that the laboratory test should take precedence if there is a clinically important discrepancy between the lab and POC NP results.

7.6. Discontinuation/Withdrawal of Participants from Study

Each participant has the right to withdraw from the study at any time. In addition, the Investigator may discontinue a participant from the study at any time if the Investigator considers it necessary for any reason including:

- Ineligibility (either arising during the study or retrospectively having been overlooked at screening)
- Withdrawal of Consent

- Loss to follow up
- Transition of heart failure care out of the primary care team

Data from withdrawn participants up to the point of withdrawal will be included in the analysis unless the participant specifies otherwise. Withdrawn participants will not be replaced.

The reason for withdrawal will be recorded in the CRF.

7.7. EQA comparison

At a single time point during the study period, EQA samples for NT-proBNP will be provided to clinicians working on the study. Clinicians will analyse these samples with the POC NP device as if they were patient-derived venous blood samples and report the results on the EQA form as staff completing quality control. The EQA comparison will not involve any participant visits, participant data, or samples from study participants.

If possible, some EQA samples will be analysed multiple times to assess precision.

7.8. Definition of End of Study

The end of study is the date of the last visit of the last participant or the last focus group. The study team will notify the main REC that the study has ended and will provide them with a summary of the clinical trial report within 12 months of the end of study.

8. SAFETY REPORTING

8.1. Definition of Serious Adverse Events

A serious adverse event 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
- consists of a congenital anomaly or birth defect.

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.

NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

8.2. Reporting Procedures for Serious Adverse Events

A serious adverse event (SAE) occurring to a participant should be reported to the REC that gave a favourable opinion of the study where in the opinion of the patient's GP the event was 'related' (resulted from administration of any of the research procedures) and 'unexpected' in relation to those procedures. Reports of related and unexpected SAEs should be submitted within 15 working days of the patient's GP becoming aware of the event, using the HRA report of serious adverse event form (see HRA website). As patients remain under their GP's care throughout the study, and serious adverse events such as death and hospitalisation unrelated to the study are expected in this patient group, no formal monitoring of SAEs will be carried out.

9. STATISTICS AND ANALYSIS

9.1. The Number of Participants

This is a feasibility study designed to test the primary outcome measure in heart failure patients. A sample of 30 patients should be sufficient to ascertain this. As this is a feasibility study, a formal sample size calculation has not been carried out, and the chosen sample size has been based on practical judgement. Prevalence of HF in the community is approximately 1-2% so for an average practice with 10,000 list size, there will be 100 pts with HF per practice. Therefore, recruiting 10 patients per practice is realistic.

The number of participants is not critical for the focus group method and not every patient or GP invited will agree to take part. However, a minimum of three participants will be required to convene a focus group meeting, and a maximum of eight people will be included in each session. We anticipate running 1 – 3 focus group sessions with patients and 1 – 3 with health professionals.

9.2. Analysis of Outcome Measures

Analyses will include all participants. Participants who withdraw consent will be included in analyses up to the point of consent withdrawal, unless they indicate that they wish to withdraw previously collected data from analysis.

Within-person and between-person variability of POC NP will be calculated using all available POC NP measurements, along with 95% confidence intervals.

The proportion of planned POC NP tests will be calculated as the number of POC NP results divided by the expected number of tests. This will be carried out for each visit (i.e. baseline, 6 months. 12 months, routine appointments), as well as over the entire study. We will carry out a similar analysis using the number of tests carried out as the numerator (as opposed to the number of available results).

The impact on decision making will be assessed as the proportion of POC NP tests for which the patient's primary care clinician states that knowledge of the POC NP result would have or did result in a change to their clinical decision-making process. This will be assessed separately for study visits and for routine appointments, as well as over the entire study.

The recruitment and retention rates will be calculated, retention rates will be assessed at both 6 and 12 months.

Acceptability of the POC NP for both patients and clinicians will be summarised using the median and interquartile range of the Likert scale responses at each time point.

Focus groups will be recorded and transcribed verbatim. Transcripts will be anonymised and a thematic framework analysis will be conducted using NVIVO 10 software, structured around the main areas of questioning but also allowing for emergent themes. Data analysis and data collection will proceed iteratively and early findings will inform questioning in subsequent focus groups. The interactions between focus group members and how this affected the content will also be analysed. Agreement between POC NP and lab NP, and EQA comparisons, will be measured using Bland Altman plots.

10. DATA MANAGEMENT

10.1. Access to Data

Direct access will be granted to authorised representatives from the Sponsor and host institution for monitoring and/or audit of the study to ensure compliance with regulations.

10.2. Data Recording and Record Keeping

The paper CRF must be completed, signed/dated and returned to the research team at the University of Oxford by the Investigator or an authorised member of the site research team (as delegated on the Site Signature and Delegation Log).

Entries on the paper CRF should be made in ballpoint pen, in blue or black ink, and must be legible. Any errors should be crossed out with a single stroke, the correction inserted and the change initialled and dated. If it is not obvious why a change has been made, an explanation should be written next to the change.

Data reported on each form should be consistent with the source data or the discrepancies should be explained. If information is not known, this must be clearly indicated on the form. All missing and ambiguous data will be queried. All sections are to be completed before returning.

In all cases it remains the responsibility of the Investigator to ensure that the CRF has been completed correctly and that the data is accurate.

The completed originals should be sent to the research team at the University of Oxford and a copy filed in the Investigator Site File.

Study forms may be amended by the research team at the University of Oxford, as appropriate, throughout the duration of the study. Whilst this will not constitute a protocol amendment, new versions of the form must be implemented by participating sites immediately on receipt.

All study data will be entered into a study specific database on password protected workstations by appropriate members of the research team. The data base will be stored on a restricted area of the file server, not the workstation.

All documents will be stored securely and kept in compliance with the Data Protection Act. Data collected on the CRFs will be stored in an electronic database in which the participant will be identified by a study specific number. Names and any other identifying details will be stored in a separate database linked only by the study number.

Focus group discussions will be audio recorded and transcribed. If participants agree, video recording may also be used to aid transcription and analysis, as it helps the researchers to know who was speaking at any particular time. Transcripts will be anonymised. Video and audio files will be deleted off the recording device once they have been downloaded to a University of Oxford server. Audio files will be encrypted and made accessible to transcribers via a secure University of Oxford server, and transcripts returned from transcribers in the same way. All transcribers will sign a confidentiality agreement with the University of Oxford. Digital audio and video recordings of the focus group interviews will be destroyed at the end of the study. The University of Oxford Nuffield Department of Primary Care Health Sciences will act as the data custodian. Publication of direct quotations from research participants may be included in project outputs, such as the final report, conference presentations and articles submitted to peer reviewed journals. However, all identifying information about participants will be removed to ensure their anonymity and to protect their identity.

11. QUALITY ASSURANCE PROCEDURES

The study may be monitored, or audited in accordance with the current approved protocol, GCP, relevant regulations and standard operating procedures.

12. ETHICAL AND REGULATORY CONSIDERATIONS

12.1. Declaration of Helsinki

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

12.2. Guidelines for Good Clinical Practice

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

12.3. Approvals

The protocol, informed consent form, participant information sheet and any proposed advertising material will be submitted to an appropriate Research Ethics Committee (REC), HRA, 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.

12.4. Reporting

The CI shall submit once a year throughout the study, or on request, an Annual Progress report to the REC Committee, HRA, host organisation and Sponsor. In addition, an End of Study notification and final report will be submitted to the same parties.

12.5. Participant Confidentiality

The study staff will ensure that the participants' anonymity is maintained. The participants will be identified only by a participant ID number on all study documents and any electronic database. All documents will be stored securely and only accessible by study staff and authorised personnel. The study will comply with the Data Protection Act, which requires data to be anonymised as soon as it is practical to do so.

12.6. 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.

In addition to travel expenses, patients attending focus groups will receive a £20 shopping voucher to thank them for their time.

12.7. Other Ethical Considerations

There is a possibility that participants in focus groups may disclose an incident of very poor care or abuse. This is considered to be highly unlikely, but in the event of such a disclosure, the researchers will report it to the appropriate authorities. Researchers will be guided by national guidelines as to what constitutes abuse.

As this is a feasibility study of point-of-care NT-proBNP in primary care, and there is currently no NICE guidance on the use of NT-proBNP for monitoring heart failure, we are not asking clinicians to incorporate either point-of-care or lab NT-proBNP results into their clinical management. However, since they will have access to both results, and it is possible that they will wish do so, or would have done so if they had access at the time of making management decisions, we are collecting data on this. In most cases, we anticipate that clinical decisions will have been made without sight of either point of care or lab NT-proBNP results, and so we will be asking about whether knowledge of the result would have changed management if it was available at the time of decision making. However, we will allow for reporting of instances where results have influenced decision making, or have resulted in changes to management once they have become available.

13. FINANCE AND INSURANCE

13.1. Funding

The study is being funded by NIHR Programme Grant for Applied Research RP-PG-1210-12003.

13.2. 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 that is provided.

14. PUBLICATION POLICY

The Investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study. Authors will acknowledge that the study was funded by NIHR and will comply with NIHR publication policies. Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged.

15. REFERENCES

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16. APPENDIX A: AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made

List details of all protocol amendments here whenever a new version of the protocol is produced. This is not necessary prior to initial REC submission.

17. APPENDIX B: SCHEDULE OF STUDY PROCEDURES

Data to be collected from patients at each time point

Data	Baseline Visit	6 Month Visit	12 Month Visit	Heart Failure Appointments
Eligibility and Consent	X			
Demographics (age, gender, ethnicity)	X			
POC NT-proBNP	X	X	X	X
Qualification of person taking POC measurement (e.g. nurse, doctor, HCA)	X	X	X	X
Sample for renal function	X	X	X	X
Sample for lab NT-proBNP	X	X	X	
Weight	X	X	X	X
Blood pressure	X	X	X	X
Pulse	X	X	X	X
Current medication	X	X (update)	X (update)	X (update)
Any changes made to medication at this appointment	X	X	X	X
Concurrent medical problems	X	X (update)	X (update)	X (update)
Type of HF	X			
Presence and type of AF	X	X	X	X
Presence of other arrhythmias	X	X	X	X
NYHA classification	X	X	X	
Minnesota Living with Heart Failure Questionnaire	X	X	X	
Likert assessment of acceptability			X	
Invitation to focus group			X	
Reason for appointment				X
Notes review			X	

Data to be collected from clinicians at each time point

Data	Following each patient visit	Following last patient visit
Study site	X	X
Clinician type (e.g. nurse, doctor, HCA)	X	X
Effect of POC NP on decision-making process	X	
Likert assessment of acceptability		X
Invitation to focus group		X

18. Appendix C: List of additional documents

1. Study invitation letter
2. Patient information leaflet
3. Study consent form

4. Focus group patient information leaflet
5. Focus group clinician information leaflet
6. Focus group patient consent form
7. Focus group clinician consent form
8. Focus group patient invitation letter
9. Focus group clinician invitation letter
10. Focus group patient reply slip
11. Focus group clinician reply slip