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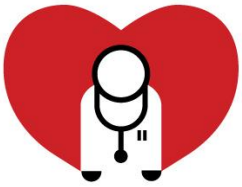

REFER

The REFER (REFer for EchocaRdiogram) Study: A Prospective Validation of a Clinical Decision Rule, NT-proBNP, or their combination, in the Diagnosis of Heart Failure in Primary Care

STUDY PROTOCOL

Version 1.4

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Chief Investigator: Professor Richard Hobbs
Professor of General Practice
Head of Department
General Practice
University of Oxford
2nd Floor, 23-38 Hythe Bridge Street
Oxford OX1 2ET

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KEY CONTACTS

Chief Investigator:
Professor Richard Hobbs
Head of Department
General Practice
University of Oxford
2nd Floor, 23-38 Hythe Bridge Street
Oxford
OX1 2ET

Tel: 01865 289288
Fax: 01865 289287
Email: richard.hobbs@phc.ox.ac.uk

Sponsor:
Mrs E Chick
Deputy Head, Clinical Trials & Research Governance
Research Services, University Of Oxford
Joint Research Office
Block 60, Churchill Hospital
Old Road
Headington
Oxford
OX3 7LJ

Tel: 01865 572227
Fax: 01865 572228
Email: Elaine.chick@admin.ox.ac.uk

Research Fellow/Senior Study Co-ordinator:
Dr Lynda Tait
Research Fellow
Primary Care Clinical Sciences
School of Health and Population Sciences
University of Birmingham
Edgbaston
Birmingham B15 2TT

Tel: 0121 414 8584
Fax: 0121 414 6571
Email: l.tait.1@bham.ac.uk

Research Fellow/Study Co-ordinator:
Mrs Rachel Iles
Research Fellow
Primary Care Clinical Sciences
School of Health and Population Sciences
University of Birmingham
Edgbaston
Birmingham B15 2TT

Tel: 0121 414 2691
Fax: 0121 414 6571
Email: r.iles@bham.ac.uk

PC-CTRU Trial Management Lead:
TBA

Trial Statistician:
Ms Andrea Roalfe
Medical Statistician
PC-CTRU
Primary Care Clinical Sciences
School of Health and Population Sciences
University of Birmingham
Edgbaston
Birmingham B15 2TT

Tel: 0121 414 7077
Fax: 0121 414 6571
Email: a.k.roalfe@bham.ac.uk

Health Economics Modelling:
Dr Pelham Barton
Health Economics
Health & Population Sciences
University of Birmingham
Edgbaston
Birmingham B15 2TT
Tel: 0121 414 3170
Fax: 0121 414 8969
Email: p.m.barton@bham.ac.uk

Study Secretary:
Ms Rebecca Green
Secretary
Primary Care Clinical Sciences
School of Health and Population Sciences
University of Birmingham
Edgbaston
Birmingham B15 2TT
Tel: 0121 415 8204
Fax: 0121 414 8616
Email: r.green.4@bham.ac.uk

Echocardiographic Technician:
Mrs Marites Derit
Echocardiographic Technician
Primary Care Clinical Sciences
School of Health and Population Sciences
University of Birmingham
Edgbaston
Birmingham B15 2TT
Tel: 0121 414 8590
Fax: 0121 414 6571
Email: m.derit@bham.ac.uk

Co-investigators:
Dr Lynda Tait
Research Fellow
University of Birmingham
Tel: 0121 414 8584
Fax: 0121 414 6571
Email: l.tait.1@bham.ac.uk

Professor Jon Deeks
Professor of Health Statistics
Public Health, Epidemiology & Biostatistics
University of Birmingham
Tel: 0121 414 5328
Fax: 0121 414 7878
Email: j.deeks@bham.ac.uk

Mrs Andrea Roalfe
Senior Research Fellow
Primary Care Clinical Sciences
University of Birmingham
Tel: 0121 414 7077
Fax: 0121 414 3759
Email: a.k.roalfe@bham.ac.uk

Professor Martin Cowie
Cardiologist
National Heart & Lung Institute
Imperial College,
London
SW3 6LY
Tel: 020 7351 8856
Email: m.cowie@imperial.ac.uk

Professor Jonathan Mant
Professor of Primary Care Research
General Practice & Primary Care Research Unit
University of Cambridge
Forvie Site, Robinson Way
Cambridge
CB2 OSR
Tel: 01223 330325
Fax: 01223 762515
Email: jm677@medschl.cam.ac.uk

Dr Pelham Barton
Senior Lecturer
Mathematical Modelling
Health Economics Unit
University of Birmingham

Tel: 0121 414 3170
Fax: 0121 414 8969
Email: p.m.barton@bham.ac.uk

Dr Clare Taylor
Clinical Academic GP
Primary Care Clinical Sciences
University of Birmingham

Tel: 0121 414 8629
Fax: 0121 414 2282
Email: c.j.taylor.1@bham.ac.uk

Study Investigators Group:

Name	Role
Professor Richard Hobbs	Chief Investigator
Rev, Dr Barry Clark	Patient Representative
Dr Lynda Tait	Co-investigator
Professor Jon Deeks	Co-investigator
Ms Andrea Roalfe	Co-investigator
Professor Martin Cowie	Co-investigator
Professor Jonathan Mant	Co-investigator
Dr Pelham Barton	Co-investigator
Dr Clare Taylor	Co-investigator

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1.0 STUDY SUMMARY

1.1. STUDY FLOW DIAGRAM

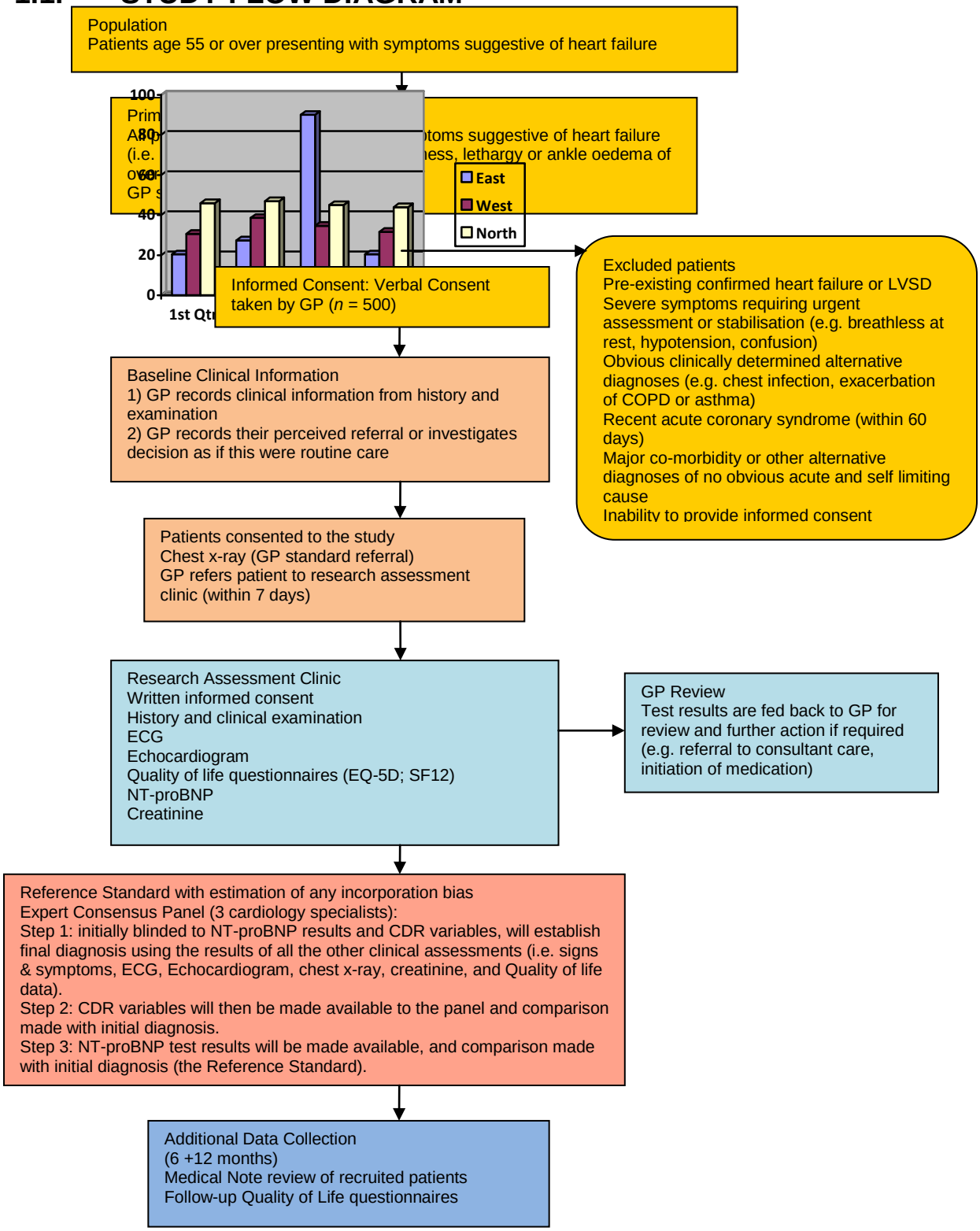

Figure 1. Flow diagram of study design, patient recruitment and data collection

2.0 GLOSSORY OF TERMS AND ABBREVIATIONS

ACE	Angiotensin-converting enzyme
AE	Adverse Event
AF	Atrial fibrillation
AUC	Area under the curve
BNP	Brain (B-type) Natriuretic Peptide
CDR	Clinical Decision Rule
CHD	Coronary heart disease
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
DMEC	Data Monitoring & Ethics Committee
ECHO	Echocardiography
ECRF	Electronic Case Report Form
ECG	Electrocardiogram
EF	Ejection fraction
GCP	Efficacy & Mechanism Evaluation programme
EME	Good Clinical Practice
HF	Heart failure
HFPEF	Heart failure with preserved ejection fraction
HTA	Health Technology Assessment
GP	General Practitioner
LREC	Local Research Ethics Committee
LV	Left ventricular
LVEF	Left ventricular ejection fraction
LVSD	Left ventricular systolic dysfunction
MidReC	Midland Research Practices Consortium
MI	Myocardial infarction
MRC	Medical Research Council
MREC	Multi-centre Research Ethics Committee
NHS	National Health Service
NICE	National Institute for Clinical Excellence
NIHR	National Institute for Health Research
NPV	Negative predictive value
NSF	National Service Framework
NT-proBNP	N-terminal proB-type natriuretic peptide
NYHA	New York Heart Association
PC-CRTU	Primary Care Clinical Research Trials Unit
PCRN	Primary Care Research Network
PCT	Primary Care Trust
PI	Principal Investigator
PPV	Positive predictive value
QALY	Quality adjusted life year
QoL	Quality of Life
R&D	Research and Development
ROC	Receiver operating characteristic
SAE	Serious Adverse Event
STARD	Standards for reporting of diagnostic accuracy

3.0 BACKGROUND

3.1. HEART FAILURE

Heart failure (HF) is a life-threatening, costly condition (1). The need for effective diagnostic and treatment strategies in HF is immense: it affects at least 2.3% of adults over 45, rising to 4% in over 75 year olds (2). HF has a major impact on patients and healthcare systems: its prognosis is worse than breast or prostate cancer (3), it markedly reduces quality and length of life (4), and treatment costs are high, second only to stroke and mainly due to high admission rates (5); estimated to consume almost 2% (£751 million) of total NHS expenditure (6). Primary care is where most of these patients initially present. However, HF is commonly misdiagnosed in this setting, with up to 50% misdiagnosed (7). HF is a diagnostic challenge, as symptoms are non-specific and physical signs can be subtle (8-11). Because outcomes in HF are linked to stage of disease and evidence-based treatments alter natural history as well as improve symptoms and prognosis (12-14), accurate early diagnosis and treatment is essential to reduce morbidity and mortality. As most patients with suspected HF are seen initially by GPs (8;15), the need for early and accurate diagnosis in primary care is essential to ensure optimum management and appropriate treatment is initiated rapidly.

3.2. DIAGNOSIS OF HEART FAILURE

Specialist review of symptoms and signs plus objective investigations, including echocardiography (Echo), is the established 'gold standard' for diagnosing left ventricular systolic dysfunction (LVSD) and increasingly suspected HF with a preserved ejection fraction (HFpEF) (1). Diagnosing HF requires objective estimation of cardiac function (i.e. Echo) since determining the aetiology and stage of HF leads to different management choices such as initiation of angiotensin-converting enzyme (ACE) inhibitors (12) and ß-blockers (13) in most patients with LVSD, spironolactone (14) in those cases with severe HF, or surgery where significant valve disease exists. These therapies improve symptoms, prognosis and quality of life, and can reduce healthcare utilisation and NHS costs. However, a difficulty is that performing Echo on all suspected HF patients would be costly as many patients are found not to have HF.

3.3. CURRENT UK PRIMARY CARE PRACTICE

Diagnostic strategies can vary between GPs if a case of HF is suspected, but the most appropriate strategy is unclear. These include an initial clinical assessment of patient signs and symptoms using physical examination, and investigations such as lab blood tests or chest x-ray. Additionally, screening tests, such as electrocardiogram (ECG) and natriuretic peptide (NP) tests, where available, have been recommended by NICE as potential 'rule out' tests for HF to limit unnecessary referrals to echocardiography (16;17). This routine clinical assessment takes place over multiple consultations, due mainly to diagnostic uncertainty and delays that occur in the referral pathway.

3.4. CURRENT HEART FAILURE REFERRAL SYSTEM

Provision of diagnostic tests varies between Primary Care Trusts (PCTs), resulting in a variety of diagnostic pathways for HF in neighbouring practices. In some areas, GPs do not have access to natriuretic peptides (NPs) as a diagnostic test despite national guidance suggesting this can be beneficial in the diagnostic decision-making process. Some PCTs have open access

Echo but the strict referral criteria introduce delays in diagnosis. For example, in South Birmingham PCT the referral criteria for the open access Echo stipulates that the patient with suspected HF must have an ECG and a chest x-ray prior to referral, and one of these tests must be abnormal. Therefore, a patient first needs to attend the local outpatient x-ray department to have a chest x-ray, which must then be reported by radiology and the report sent through to the GP. The patient must also attend the practice to have an ECG, which must be reported either in-house or faxed through to the local cardiology department for interpretation. If both tests are normal then a diagnosis of HF is thought to be unlikely. If the GP still suspects HF, a referral to secondary care for cardiology review can be done, using the usual referral process through the Choose and Book system.

3.5. BARRIERS TO ACCURATE DIAGNOSIS OF HEART FAILURE IN PRIMARY CARE

Diagnostic uncertainty in clinical practice, difficulties diagnosing HF and local organisational factors such as limited availability of diagnostic services, or delays inherent in the current referral system, create barriers to the early and accurate diagnosis of HF. Access to Echo is variable, often delayed, and limited by the significant skill shortage of trained echocardiographers (1;16;18;19). As a consequence, many GPs rely solely on, often inaccurate, unstructured clinical assessment (9;10;18;20). However, diagnosing HF on clinical grounds alone can be unreliable due to difficulty in interpreting signs (21) and differences between doctors in obtaining symptoms and signs (15;22). Many GPs order a chest x-ray, or arrange an ECG (9). However, although a normal ECG will exclude LVSD in most cases, changes may be subtle and lack of GP interpretation skills may still require referral for specialist opinion. A normal chest x-ray does not exclude HF (23). A key dilemma facing GPs is deciding which patients to refer for Echo and when; and lack of a systematic method for guiding the diagnosis of HF presents a further obstacle (9), adding to cost and delay. Diagnostic uncertainty or inaccurate diagnosis can result in diagnosis being delayed until HF symptoms are more obvious and therefore more severe, multiple GP consultations and hospital admissions, or people are treated incorrectly.

3.6. ALTERNATIVE DIAGNOSTIC METHODS

A growing body of evidence suggests the potential utility of B-type natriuretic peptides (NPs), namely BNP or NT-proBNP, both released from myocardium in response to wall stretch, as diagnostic cardiac biomarkers of HF. These NP tests provide an exciting opportunity to support the clinical assessment of symptomatic primary care patients, as normal levels can rule out HF given the high sensitivity of these tests (98%) (24), but confirmatory Echo is needed in patients with elevated peptides to confirm the diagnosis (24-28).

3.7. NATRIURETIC PEPTIDES AND UNCERTAINTY

There is uncertainty about the best cut-off levels of NPs in primary care and the cost-effectiveness/benefit has not been established. NP testing is under-used because reliable data on BNP and NT-proBNP performance in the diagnosis of HF are limited mainly to epidemiological sub-studies or to prospective validation in emergency department settings (27;29-31), with limited data on test performance within symptomatic patients routinely presenting in primary care (24;28;32). Best assay cut-offs have therefore been largely imputed and assay performance against or with ECG and symptom score unclear. Moreover, obesity and certain HF medications can lower peptide levels and elevated levels can be associated with unrelated conditions and other factors such as increased age, gender and renal insufficiency (25). These factors therefore impair the utility of NPs as a diagnostic marker of HF if used alone. The addition of a B-type NP test to the current diagnostic pathway, with specialist referral if test

results are abnormal, is a suggested alternative approach that may be superior and cost-effective (33). However, the cost-effectiveness of NPs versus standard diagnostic triage is not established.

Current consensus suggests that a superior approach would be to combine NP testing with standard clinical assessment. In a recent prospective, randomised controlled trial of 305 elderly patients with symptoms of recent onset breathlessness or oedema GP diagnoses were more accurate with NT-proBNP test results in addition to routine clinical assessment than without, mainly due to the ability to correctly rule out HF (28). A recent meta-analysis concluded that the use of NPs could help reduce the demand for Echo and cardiology referrals (34). However, determining the optimal manner in which to combine clinical features from clinical assessment and diagnostic tests, including NP tests, remains extraordinarily challenging.

3.8. DECISION-MAKING TOOLS

Clinical decision rules (CDRs) are evidence-based clinical tools designed to be used to help clinician decision-making in a standardised and cost-effective manner, and are developed according to strict methodological procedures (35;36). These clinical tools are based on a parsimonious set of variables that can quantify the contribution from history, physical examination and diagnostic tests. They are developed and evaluated in three distinct stages prior to implementation into a clinical setting: 1) creation of the rule, establishing the independent and combined effect of explanatory variables such as symptoms, signs or diagnostic tests; 2) validation of the rule, establishing the accuracy and reliability of the tool in a separate population; and 3) impact analysis of the rule, establishing impact of applying the rule on patient outcome or health professional behaviour.

A number of CDRs have been developed to diagnose HF, using combinations of signs, symptoms and tests (37-39). However, a major problem with all the studies is spectrum and referral bias since most were based on observational screening studies rather than symptomatic presenting patients and some were hospital rather than community based. Additionally, the tools are impractical outside a research or emergency department setting as they are based on a substantial number of variables; others rely on clinical signs where there is considerable inter-observer variation, even amongst specialists; and others rely on chest x-ray parameters, which would be difficult to apply in general practice.

Our recent NIHR HTA funded systematic review and independent patient data and meta-analysis (40) addressed this issue. We found individual symptoms (such as breathlessness and fluid retention) and signs (such as resting tachycardia and raised jugular venous pressure) are generally weak predictors of HF. Both ECG and BNP have high sensitivity for HF and are good tests at ruling out the diagnosis but BNP is more accurate than ECG. We found BNP and NT-proBNP to be of similar accuracy.

Our systematic review (40) identified one unpublished study which had developed a decision tool based on simple clinical features (41). In our individual patient data analysis (40) we further developed this tool and validated it on other primary care data sets. We found that a simplified model, based upon simple clinical features (Male gender, history of myocardial Infarction, basal Crepitations, oEdema: 'MICE') and BNP derived from one data set, was found to have good validity when applied to other data sets, with the area under the curve between 0.84 and 0.96, and reasonable calibration. A model substituting ECG for BNP was less predictive. Our systematic review concluded that BNP could substitute for ECG for determining referral to Echo and some patients could be referred with no prior tests on the basis of clinical features alone.

4.0 RATIONALE FOR CURRENT STUDY

In developing and validating the current CDR, we have addressed the aforementioned limitations of previous validation studies of CDRs for HF. The purpose of the REFER study is to perform a rigorous evaluation of the clinical validity and diagnostic utility of the CDR, including assessment of the incremental value of combining clinical findings from clinical history and examination and diagnostic testing (i.e. NP testing) in a new and symptomatic primary care patient population.

Considerable advances have been made in understanding the potential utility of natriuretic peptides as cardiac biomarkers, in outpatient and emergency care settings and more recently in primary care. For primary care patients suspected clinically of having HF it is important to identify the best diagnostic strategy to identify early in the diagnostic process those who need confirmatory assessment followed by appropriate treatment. There is agreement that B-type NP measurement has added value as a 'rule out' test for HF, but the optimal predictive value of varying cut-off levels is unclear in the primary care setting. The usefulness of B-type NP testing in combination with clinical information in the diagnostic assessment of suspected HF in primary care settings is also not yet adequately addressed.

We shall also establish the clinical utility of B-type NP tests in informing the diagnosis of diastolic HF as well as LVSD and valve disease. Additionally, we shall determine the probability thresholds of the CDR above which Echo would be the most cost-effective diagnostic strategy, taking into account patient quality of life and survival. The results will contribute to scientific progress by solving the problem wherein GPs have clinical uncertainty about whether an Echo should be done or not for a patient whom they suspect may have HF. There is now an opportunity to provide these data and to potentially demonstrate that the CDR can improve patient management concerning diagnostic accuracy, clinical decision-making and cost-effectiveness.

Our proposal will build upon the current evidence and address the weaknesses in previous work. We have validated the CDR on primary care data sets but further validation in a symptomatic population in the real-life clinical setting is now indicated. Further exploration of the optimal NP cut-offs and further modelling of cost-effectiveness is also needed. We aim to prospectively validate the CDR in this study but GPs will not apply the CDR (applying the rule would be appropriate in an implementation study); GPs will refer all patients suspected of having HF and not previously diagnosed with Echo and we shall collect data on how well the CDR predicts the diagnosis of HF. The CDR's impact potential will be demonstrated by evaluating whether its sensitivity and specificity is superior to that of GPs' (unaided) decisions. Given the risk of delayed diagnosis of HF, GPs do not have clear guidance on whom to refer for further evaluation. Improving the ability of GPs to appropriately identify patients suspected of having HF is crucial not only to avoid unnecessary hospital admissions and reduce patient burden, but also to improve the quality of care for patients presenting to primary care with suspected HF.

5.0 AIMS AND OBJECTIVES

The primary aim of this study is to prospectively validate a CDR, a natriuretic peptide assay, or their combination, in the diagnosis of suspected HF in primary care. Secondary aims are to determine if the CDR or assay can be used in routine clinical practice to establish referral on for echocardiography in patients presenting with symptoms suggestive of HF and to quantify the most reliable cut-off level of the natriuretic peptide assay in this group of symptomatic presenting patients. The specific objectives are designed to provide a comprehensive assessment of the validity of the CDR.

5.1. OBJECTIVES

We propose the following objectives:

- To prospectively validate the performance of the CDR and compare it to using a natriuretic peptide assay alone on the diagnostic accuracy of HF in primary care
- To determine if the CDR, or natriuretic peptide assay can be used in routine clinical practice to establish referral on for echocardiography in patients presenting with symptoms suggestive of HF
- To quantify the most reliable cut-off levels of the natriuretic peptide assay in a group of symptomatic presenting patients
- To model the cost-effectiveness of using the CDR in primary care

6.0 DESIGN

6.1. STUDY DESIGN AND SETTING

REFER is a prospective, observational, diagnostic validation study of a CDR, natriuretic peptide or their combination, for diagnosing heart failure in primary care. Consecutive primary care patients with a chief complaint of recent new onset shortness of breath, lethargy, or peripheral ankle oedema of over 48 hours duration will be enrolled. The study will be conducted in 20 urban and rural primary care practices in Birmingham, West Midlands, England.

The study will adhere to methodological standards for the validation of clinical decision rules that recommend use of objective outcome variables, appropriate validation techniques, and assessment of the accuracy of the rule by validation in an independent, symptomatic patient population. Our reference standard procedure is independent from the test results (i.e. an independent expert panel will make the final HF diagnosis). We shall report the study findings in accordance with STARD guidelines (42;43). A strength of our study is the inclusion of <u>all</u> consecutive consenting primary care symptomatic patients. No bias will be introduced as the Reference Test will be applied in <u>all</u> patients.

6.2. MINIMISING POTENTIAL BIAS

The studies we uncovered in our systematic review (40) had pronounced methodological and design weaknesses, especially in regard to spectrum and referral bias, since most were based on observational screening studies rather than symptomatic presenting patients and were hospital rather than community based. Only a prospective study design with consecutively recruited symptomatic patients can avoid or minimise these and other potential biases, such as verification bias. Our design allows us to ensure that all symptomatic patients presenting with new onset symptoms will be included and receive identical standardised assessments and diagnostic verification of HF. This will ensure that all patients are diagnosed in a consistent way to avoid introducing variation into the reference standard. The reference standard incorporates multiple assessments, minimising potential reference standard misclassification (44).

Incorporation bias has implications for the design of reference tests. This occurs when knowledge of the results of the index test (decision rule) influences the reference standard test (final diagnosis). To minimise this source of bias, we shall present all clinical and test information to the independent expert panel in 3 steps. This will allow us to: 1) quantify the effects of incorporation bias; 2) explore the impact that availability of NT-proBNP result would have on the reference standard diagnosis of HF. This latter analysis is of clinical significance. The current NICE algorithm for HF diagnosis envisages NPs used principally as a triage test to determine which patients should have Echo. However, in diagnosis of HF with preserved

ejection fraction, it may be that a raised NP is of diagnostic value in its own right. We are evaluating this within our study.

6.3. STUDY POPULATION

All adult primary care patients aged 55 years or over presenting to their GP with recent new onset symptoms of breathlessness, lethargy or ankle oedema of over 48 hours duration, with no obvious acute and self-limiting cause, will be enrolled.

All consenting patients meeting the eligibility criteria are entered into the study. All patients will undergo a structured clinical assessment, as we have done previously in our ECHOES (2) study and our ongoing follow-up ECHOES-X study. GPs will refer all eligible patients, whether or not they believe HF is a likely diagnosis, to a research team led clinic, where all clinical assessments will be performed up to seven days later.

7.0 ELIGIBILITY

The eligibility criteria will be confirmed by investigation and specialist interpretation of clinical assessments. Objective evidence of HF (reference standard) will be determined by a specialist panel that will validate previous diagnosis and investigations.

7.1. INCLUSION CRITERIA

Patients meeting the following criteria are eligible for study entry:

- All patients 55 years of age or over presenting to their GP with new onset symptoms of breathlessness, lethargy or ankle oedema of over 48 hours duration, with no obvious recurrent, acute or self-limiting cause.
- Able to give informed consent

7.2. EXCLUSION CRITERIA

Patients meeting any of the following criteria are not eligible for study entry:

- All patients with known pre-existing heart failure or left ventricular systolic dysfunction of any cause. However, patients with a pre-existing label of heart failure but without objective evidence (i.e. echocardiography) of this will not be excluded
- Severe symptoms requiring urgent assessment or stabilisation (e.g. breathless at rest, hypotension, confusion)
- Obvious clinically determined alternative diagnoses such as chest infection, exacerbation of chronic obstructive pulmonary disease or asthma
- Recent acute coronary syndrome (within 60 days)
- Major co-morbidity or other alternative diagnoses of no obvious acute and self-limiting cause (e.g. malignancy, severe respiratory disease, renal diagnosis, mental health problem)
- Unable to provide informed consent

8.0 RECRUITMENT PROCESS

8.1. INFORMED CONSENT

Potential participants presenting to GPs with symptoms suggestive of HF will receive a verbal explanation of the study and the Patient Information leaflet, which outlines the purpose and procedures of the study. GPs will carefully explain the benefits and potential risks to patients and inform them that they can withdraw from the study at any time and without it affecting their medical treatment. Patients will be formally assessed for eligibility and invited to provide verbal consent by GPs. We have chosen to seek research recruitment during the GP consultation because the patient's condition will be acute (breathlessness, lethargy or ankle oedema) and therefore the patient cannot be expected to delay the decision to provide verbal consent. The right of the patient to refuse consent without giving reasons will be respected. Written consent will be taken at the research assessment clinic to allow the patient time to consider participation in the study. Consent will also be sought for access to patient medical records. Patients who decline to take part in the study will be managed as usual practice by GPs. If a patient withdraws consent during the study and consent for use of their data, they will be confidentially destroyed.

8.2. SCREENING AND RECRUITMENT OF PATIENTS

GPs will screen potential participants aged over 55 years who present with target symptoms which may be suggestive of HF (new onset shortness of breath, lethargy, or ankle oedema of over 48 hours duration) and who have not been previously diagnosed with Echo. GPs will determine patient eligibility using clinical history and examination, and then complete a web-based Case Report Form. This form contains the inclusion and exclusion criteria, with tick boxes for easy completion, which GPs must complete to verify patient eligibility. GPs will give the patient a written study information sheet that outlines the nature of the study, including information about possible benefits and risks, research ethics committee approval, and advice that they can decline to participate or withdraw at any time without this affecting their medical care. The GP will then obtain verbal consent; full informed written consent will be taken by the research nurse subsequently at one of our two research assessment clinics.

8.3. REFERRAL OF PATIENTS TO RESEARCH ASSESSMENT CLINICS

GPs will refer all eligible patients who have given verbal consent to participate in the study to one of our 2 research assessment clinics in two ways by: 1) asking the patient to telephone our research team administrator to arrange an appointment within 7 days of the initial GP consultation, or the GP obtains patient contact details for entry into the GP electronic database and the study team telephones the patient; and 2) GP completion of eligibility criteria onto the web-based Case Report Form will act as a referral letter, which we shall check to confirm eligibility and to ensure that the patient has contacted the research assessment team. If a patient changes their mind between agreeing to participate at the GP consultation and before attending their appointment at the research clinic, they are advised that they can cancel by telephoning either the research team or their GP. The patient can then re-consult with their GP if necessary. Patients who decline to take part in the study will be managed as usual practice by GPs. When eligible patients decline to participate in the study or patients do not meet entry criteria for the study, GPs will complete a weekly electronic notification form of these details. These data will be used to assess potential selection bias.

8.4. PROTOCOL COMPLIANCE AND LOSS TO FOLLOW-UP

Obtaining sufficient patient recruitment and protocol adherence can be a major problem for studies. Fostering collective ownership of the study and long-term commitment improves the likelihood of it being completed successfully. Our approach incorporates the best advice from the literature. Initial meetings with GPs will allow questions to be answered and foster collective ownership. We shall be in contact with GPs weekly, to collect data on non-participants, and this level of contact will serve to maintain commitment to the study. To maximise recruitment, we shall ensure that the web-based Case Report Form is simple and easy to use and practices are appropriately reimbursed for additional consultation time. We will also program practice computers to activate a 'pop up' on GP consultation screens, to be activated if patients have study eligible symptoms entered into their surgery case notes. To also maintain motivation, visual aids for GPs' notice boards have been created and study progress and inclusion rate will be provided in monthly newsletters. Research participants' commitment will be fostered by providing understandable patient information sheets, questionnaires with clear instructions, and reminders letters sent to non-responders for questionnaire completion.

9.0 STUDY INTERVENTIONS

9.1. CLINICAL DECISION RULE

The CDR, developed from our HTA individual patient data and meta-analysis (40), intended to be used at the start of the diagnostic pathway in primary care (45), states: in a patient presenting with suspected symptoms of HF, refer straight for echocardiography if the patient has any one of: history of myocardial infarction, or basal crepitations, or ankle oedema in a male. Otherwise, carry out a NP test and refer straight to echocardiography depending on those results interpreted in the light of clinical features indicated in the CDR (Figure 1).

a) Refer straight for echocardiography if the patient has any one of:

A history of MI
OR
Basal crepitations
OR
Ankle oedema in a male

b) Otherwise, carry out a BNP/NT-proBNP test, and refer straight for echocardiography if BNP/NT-proBNP level is above one of three cut-offs set by gender/symptoms recorded in the clinical rule:

Female without ankle oedema, refer if BNP > 210-360 pg/ml depending upon local availability of echocardiography (or NT-proBNP > 620-1060 pg/ml)
OR
Male without ankle oedema, refer if BNP > 130-220 pg/ml (or NT-proBNP > 390-660 pg/ml)
OR
Female with ankle oedema, refer if BNP > 100-180 pg/ml (or NTproBNP > 190-520 pg/ml)

Figure 1. Clinical Decision Rule

10.0 DATA COLLECTION/ASSESSMENTS

10.1. ASSESSMENT TIME POINTS

We shall use the HF diagnostic assessment procedure that we have used successfully for our ECHOES (2) study and our ongoing follow-up ECHOES-X study. Baseline assessments will take place within 7 days of GP screening of eligible patients at 2 research assessment clinics, one North and one South Birmingham to facilitate patient accessibility. 7 days was chosen as all patients will be symptomatic and therefore timely assessment is necessary. We shall perform a comprehensive clinical examination on all patients. This strategy will ensure that all patients are diagnosed in a consistent way to avoid introducing variation into the reference standard (46;47). We shall collect quality of life data and review medical notes at 6 and 12 months for health economic analysis.

10.2. DATA COLLECTION FORMS

An electronic data collection form (eCRF) with built-in safeguards to ensure data quality will be used to collect data.

All participants will be identified by a unique 4-digit ID number and each GP practice is given a 3-digit code number. All data are encrypted when transferring data from the study field to the data manager at the university should this be necessary. Study data will be entered directly onto electronic databases (computer based case report form) with built in safeguards to ensure data quality and security, in line with appropriate information technology guidelines, with data corrections electronically recorded to enable a clear audit trail. Access will be via a CITRIX thin client server with high-level encryption and sophisticated security attributes.

10.3. CLINICAL JUDGMENT ASSESSMENT

During the initial consultation, GPs will have identified a patient as eligible for referral to one of the two research assessment clinics (i.e. recent new onset shortness of breath, lethargy, or ankle oedema of over 48 hours duration). They will then complete the two clinical judgment sections of the online web-based Case Report Form: 1) details of symptoms, history and patient information, including the predictive clinical features of the CDR; 2) whether they would have made a clinical diagnosis of HF or not and what they would have done routinely with this patient (i.e. investigate, initiate referral, treat, follow-up). Following diagnostic assessment at the research assessment clinic the NP results will be fed back to GPs and based on those results, GPs will be asked what they would do (refer or not refer to Echo) and if they would amend their original diagnosis.

10.4. DIAGNOSTIC ASSESSMENT

The GP will have arranged for all patients to receive a chest x-ray when consenting patients for referral (as is usual practice). Within 7 days of referral, the research assessment clinical team will obtain written informed consent, collect baseline demographics, administer quality of life questionnaires (EQ-5D and SF12), clinically assess patients, perform a 12-lead ECG and Echo, and take blood for NT-proBNP, along with creatinine for a renal dysfunction test, calculating an eGFR (serum profile). The clinical assessments will be made by a research nurse or clinical research fellow trained in these assessments, including phlebotomy, auscultation and chest examination. The heart sounds and chest sounds for each patient will be recorded digitally and a random sample validated by a senior cardiologist blinded to the assessment clinic findings. If

the research team believes an early decision on management needs to be taken on the basis of the patient's symptoms or signs at the research assessment clinic, or the results of any of the investigations, an urgent specialist referral will be organised via the patient's GP. After we have received the GPs' clinical judgment in the Case Report Form on what they would do (refer or not refer to Echo), all test results will be made available to GPs.

10.5. ECG ASSESSMENT/INTERPRETATION

A 12-lead ECG will be performed and analysed with diagnostic software and double reported and interpreted by the echocardiographic technician and a blinded consultant cardiologist, blinded to each other's interpretation, the software interpretation and other data (i.e. symptoms, Echo, chest x-ray, NT-proBNP results). Inter-observer variability will be recorded and analysed.

10.6. ECHOCARDIOGRAPHIC ASSESSMENT

The Echos will be performed in the standard manner by a single trained BSE Accredited Echocardiography Technician, using a portable high-quality Vivid i Ultrasound machine. The Echo assessment with objective assessment of LV dimensions and ejection fraction, measurement by an area-length method, will be extended to include assessment of diastolic dysfunction. Echo results, together with clinical assessment results, will be used to establish the final diagnosis, as the reference standard (see Reference Standard Section).

The echocardiographic assessment with objective assessment of left ventricular dimensions and ejection fraction measurement by an area-length method as in our initial ECHOES (2) study will be extended to include assessment of diastolic dysfunction as follows:

Parasternal Long Axis Views (each view 3 cardiac cycles). PLAX of left ventricle with enough depth to see descending aorta; PLAX of left ventricle , aortic valve , mitral and ascending aorta; Colour Doppler of aortic and mitral valves; Measurement of left ventricular outflow (on zoom) if indicated; M-mode of aortic root and left atrium; M-mode of left ventricle; 2D measurement of left ventricle if indicated; M-mode of mitral valve; PLAX of Tricuspid Valve; Zoom of tricuspid valve; Colour of tricuspid valve; Continuous wave Doppler of tricuspid regurgitation.

Parasternal Short Axis Views (each view 3 cardiac cycles). PSAX of aortic valve; Zoom of AV if indicated; Colour of aortic valve; PSAX of mitral valve; PSAX of LV at papillary muscle level; Colour of tricuspid valve; Continuous wave Doppler of tricuspid regurgitation; PSAX of RVOT, pulmonary valve and pulmonary artery; Colour of pulmonary artery-Measure jet width and length of PR jet; Continuous wave Doppler of pulmonary artery flow; Pulsed wave Doppler and Continuous wave Doppler of RVOT.

Apical Four Chamber (each view 3 cardiac cycles). 2D image of Apical 4 chamber with enough depth to see behind the left atrium; 2D image of LV with reduced depth; Colour flow of mitral, aortic and tricuspid valve; Measure of left atrial and right atrial size; Spectral Doppler (Pulsed wave) of mitral inflow with appropriate measurements(2 clips each); Spectral Doppler (Pulsed wave) of left ventricular outflow tract for Vmax and trace of VTI; Spectral Doppler (Continous wave) of aortic valve for Vmax and trace VTI; Spectral Doppler (Pulsed Wave) of pulmonary vein flow with appropriate measurements (2 clips each); M-mode mitral inflow propagation velocity with appropriate measurements; Tissue Doppler of mitral valve annulus at septum and lateral wall (2 clips each).

Apical 2 Chamber (each view 3 cardiac cycles). 2D image of left ventricle with enough depth to see behind the left atrium; 2D image of LV at reduced depth; Colour flow of mitral valve.

Apical Long Axis (each view 3 cardiac cycles). 2D image of left ventricle with enough depth to see behind the left atrium; 2D image of LV at reduced depth; Colour flow of aortic and mitral valve.

Subcostal Long Axis View. 2D image of heart with enough depth to see behind left ventricle.

Subcostal Short Axis View. 2D image or M-Mode of IVC with a sniff.

10.7. QUALITY OF LIFE ASSESSMENT

Quality of life questionnaires will be self-administered at the initial research assessment clinic and follow-up questionnaires will be mailed to patients at 6 and 12 months to provide data for health economic modelling. Based on the procedure for our ECHOES(2) and ECHOES-X studies, we shall check patient registration status with practice managers before sending follow-up questionnaires to patients.

The EuroQol 5D (EQ-5D) Questionnaire: The EQ-5D is a widely used patient-based generic questionnaire for self perceived health assessment(48).There are five domains, including mobility, self care, main activity (i.e. work), leisure activity, pain and anxiety. It describes health-related quality of life, giving a single index score for each health state measured that can be combined to generate a single index where 1 = perfect health and negative scores represent poorer states of health.

SF-12 Questionnaire: The SF-12 is a widely used and validated short generic questionnaire for measuring health related QoL(49) and has been validated for measuring QoL of patients with cardiovascular disease(50).

10.8. BLOOD COLLECTION/BIOMARKER ASSESSMENT

We shall collect a blood sample by venepuncture to perform a point of care NT-proBNP test using a Cobas h 232 Reader and Roche Diagnostics CARDIAC proBNP test strips, for immediate results, and to perform a serum creatinine test to exclude renal dysfunction and calculate an eGFR (serum profile).

10.9. MEDICAL NOTE REVIEW

Medical note review from GP notes on recruited patients will be performed at 6 and 12 months. Data on medications, hospital and nursing home admissions, A&E attendance, referrals, presentation with new symptoms/complications, and death will be recorded. These data will be used in the economic modelling of outcomes associated with using the CDR.

10.10. WITHDRAWAL OF CONSENT

If a patient withdraws their consent during the study and consent for use of their data, they will be confidentially destroyed immediately.

11.0 REFERENCE STANDARD FOR PRESENCE/ABSENCE OF HEART FAILURE

An independent expert consensus panel comprising three cardiology specialists will determine the final diagnosis of LVSD or not (ejection fraction <40%) and HF or not, based on internationally accepted definition(1), with differences resolved by consensus. In order to reach an accurate diagnosis the consensus panel need all clinical and test information but this could introduce incorporation bias. To minimise this but provide fuller information for the consensus panel they will receive information in 3 steps. In Step 1, Echo results will be provided along with all other clinical information except the NT-proBNP test results and clinical variables included in the CDR, namely, history of myocardial infarction, gender, basal lung crepitations and ankle oedema. The consensus panel will reach a decision on whether or not HF is present initially without these data. In Step 2, CDR clinical variables will then be made available to the expert panel and comparison made with the initial assessment. In Step 3, NT-proBNP test results will be provided and the consensus panel asked whether this changes their opinion. The primary reference standard for the study is therefore Step 3 where all clinical and test information is available to the consensus panel. However, we will also be able to accurately estimate any incorporation bias that may have related to this reference standard based upon Steps 1 and 2.

11.1. DEFINITION OF HEART FAILURE

Clinical HF will be defined using the European Society of Cardiology guidelines: “HF is a syndrome in which the patients should have the following features: symptoms and signs of HF and objective evidence of an abnormality of the structure or function of the heart at rest”(1).

12.0 SAFETY REPORTING

12.1. GENERAL DEFINITIONS

12.1.1. ADVERSE EVENT

An Adverse Event (AE) is any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product, treatment or device, and which does not necessarily have a causal relationship with this treatment.

An AE can be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease in any subject in a clinical trial (including those in an untreated control group), whether or not considered related to the investigational medicinal product, treatment or device.

12.2. SERIOUS ADVERSE EVENTS (NON-IMP STUDIES)

A Serious Adverse Event (SAE) in a non-CTIMP study is defined as an untoward occurrence that:

- Results in death
- Is life-threatening*****
- Requires hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Consists of a congenital anomaly or birth defect, OR
- Is otherwise considered medically significant by the investigator

*Life-threatening in the definition of a SAE refers to an event in which the patient 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.

12.3. RECORDING AND REPORTING ADVERSE EVENTS

Procedures have been established to monitor and report Patient Safety Incidents, Adverse Events and Serious Adverse Events (SAEs) in line with guidance that applies to non-IMP studies, the Research Governance Framework 2005, and Sponsor and Primary Care Clinical Research Trials Unit (PC-CRTU) Standard Operating Procedures. In accordance with non-IMP studies, a SAE is defined as an untoward occurrence that (a) results in death; (b) is life-threatening; (c) requires hospitalisation; results in disability; (d) considered medically significant. At the end of each study visit and at 6 month follow-up contact, participants will be asked if they have experienced any untoward medical occurrence. Adverse event forms will be completed if such an event has been experienced. All SAEs will be reported within 24 hours of awareness of an event to the Sponsor and reported to the main Ethics Committee, in accordance with regulatory and ethical requirements.

13.0 OUTCOME MEASURES

13.1. PRIMARY OUTCOMES

- Test performance of the CDR, estimating the sensitivity and specificity, positive predictive value (PPV) and negative predictive value (NPV) of the CDR for diagnosis of HF in symptomatic patients presenting with shortness of breath, lethargy, or ankle oedema of over 48 hours duration
- Test performance of the diagnostic accuracy of NT-proBNP for diagnosis of HF in symptomatic patients, including sensitivity, specificity, PPV and NPV
- Proportion of patients with LVSD or not (ejection fraction <40%) and HF or not

13.2. SECONDARY OUTCOMES

- Combination of the CDR and NT-proBNP
- Modelling of CDR test performance and epidemiological data to ascertain the most cost-effective strategy in the diagnosis of HF in primary care, incorporating data on quality of life (EQ-5D and SF12 widely used questionnaires), clinical events and health care resource use
- Reliability of GP clinical judgment alone in diagnosing HF
- Reliability of individual clinical features
- Reliability of ECG interpretation
- Estimation of the best performing cut-offs for NT-proBNP to maximise diagnostic yield and for maximising cost-effective referrals
- Determine the use of variable echocardiographic markers of diastolic function in the diagnosis of HF with preserved ejection fraction

14.0 STATISTICAL ISSUES

14.1. SAMPLE SIZE

Twenty urban and rural general practices in the West Midlands will be asked to recruit 500 symptomatic patients. A search of routine practice morbidity data suggest that in a practice of

6,000 patients, around 60 patients over age 55 per year will present with new onset breathlessness. Breathlessness is the commonest of the three most likely symptoms of HF (others are lethargy or ankle swelling) and therefore these estimates on the rate that symptoms present will be the minimum rates. Assuming a 60% (conservative) response rate then it will take at least 9 months to recruit 25 such patients per practice. We shall work with 10 practices for eighteen months. Nine months after the study has started, a further 10 practices will commence patient recruitment. All practices will stop active patient recruitment at the end of 18 months. Calculations are based on sensitivity of 94% and specificity of 48% obtained from application of the CDR in our HTA funded individual patient data and meta-analysis and the prevalence of HF in a symptomatic population of 30%. A sample size of 500 patients with HF symptoms will therefore be sufficient to estimate the sensitivity of the CDR to within 4% and specificity to within 6% at the 95% confidence level.
We have now recruited 20 practices via the Midlands Research Practices Consortium (MidReC) and the Primary Care Research Network (PCRN) Central England. The practices were selected after stratification by IMD (Index of Multiple Deprivation 2007) quartile to ensure a range of socio-economic status is represented.

14.2. ACCRUAL

The inclusion criteria are not restrictive. We consider that all adults over age 55 who consult GPs with new onset symptoms of breathlessness who can benefit from more objective diagnostic methods in diagnosing cases of suspected HF are potential participants in this study. We have already recruited the general practitioners, all of whom have shown enthusiasm for evaluating a novel CDR to improve the diagnosis of patients suspected of having HF. We aim to recruit 500 patients, with a target recruitment rate of 3 patients per practice, per month. We expect to complete recruitment within 18 months. We shall monitor weekly recruitment rates and reasons for non-recruitment as part of our comprehensive monitoring plan. Deviation from the expected target accrual rate will be addressed by site visits and additional practices invited to participate, if necessary.

15.0 STATISTICAL ANALYSIS

Patients with symptoms of HF that are referred to Echo via the CDR will be classed as Test disease present and the remaining patients classed as Test disease absent. The Observed disease present or absent will be determined by the expert panel following Echo and other clinical assessments. Crosstabulation of Test versus Observed disease status will enable calculation of sensitivity (true positive rate), specificity (true negative rate), positive predictive value (PPV: proportion with a positive test result who actually have the target condition), negative predictive value (NPV: proportion with a negative test result who do not have the target condition), and likelihood ratios for testing the performance of the CDR. 95% confidence intervals for these performance statistics will be calculated using the binomial exact method.

To confirm whether the NT-proBNP cut-offs in the CDR are optimal in the real life clinical setting, an additional ROC curve analysis of NT-proBNP to predict HF will be performed. Analysis will compare the CDR performance against the step 1 reference test alone; against the step 1 reference test plus clinical features of the CDR (step 2); and against the step 1 reference test plus the CDR and the NT-proBNP result (the reference standard, step 3). Step 3 is the primary reference standard for analysis. This will allow us to: 1) quantify the effects of any incorporation bias; 2) explore the impact that availability of NT-proBNP test result would have on the reference standard diagnosis of HF. Comparison of the GPs' and researcher's clinical findings (lung crepitations, ankle oedema, decision to refer to Echo) will be assessed by the kappa statistic. Logistic regression will be used to identify which diastolic parameters of echocardiography are independently associated with the diagnosis of heart failure with preserved ejection fraction.

16.0 HEALTH ECONOMIC ANALYSIS

A decision tree will be used to assess the cost-effectiveness of the CDR(51). This will be built upon the outline tree shown in Figure 2. The prevalence of HF in patients presenting to primary care will be determined both from the study cohort and from a review of the epidemiological literature. The probability that patients with and without HF will be referred for echocardiography will be determined based on the test characteristics of both the CDR and of existing practice. The decision tree may be further refined depending on the power of the available data from the study; for example, distinguishing between patients with HF of different levels of severity (such as left ventricular systolic dysfunction and heart failure with preserved ejection fraction patients).

Cost and quality of life implications for patients at different branches of the decision tree will be extrapolated based both on data collected during the study and from the literature. Prospectively collected data on quality of life, clinical events and health care resource use will be used to estimate outcomes associated with using the CDR, NT-proBNP, their combination, or continuing with current practice. Since the study does not capture the full details of every acute event in the cohort, the cost and quality of life implications of such events will be imputed from the literature and standard UK sources of health economic information (52;53). Outcomes associated with current practice will be estimated by using GP reported clinical judgment to predict their intentions for patients in the absence of using the CDR. In addition, the model will allow exploration of the effect on cost effectiveness of hypothetical scenarios involving altering the threshold peptide value for referral to echocardiography. Decreasing the threshold will cause more people to be referred for echocardiography, hence increasing costs but also improving outcomes. By using a suitable threshold cost per QALY cut-off (such as the threshold of £20,000 - £30,000 used by the National Institute of Health and Clinical Excellence) (54), the optimal threshold peptide value for referral can be estimated (55).

Costs will be evaluated from a health care provider perspective, with a lifetime time horizon. The effect of uncertainty in parameter values will be quantified by both univariate and probabilistic sensitivity analysis and will be summarised using appropriate methods (cost-effectiveness plots and/or cost-effectiveness acceptability curves) (51).

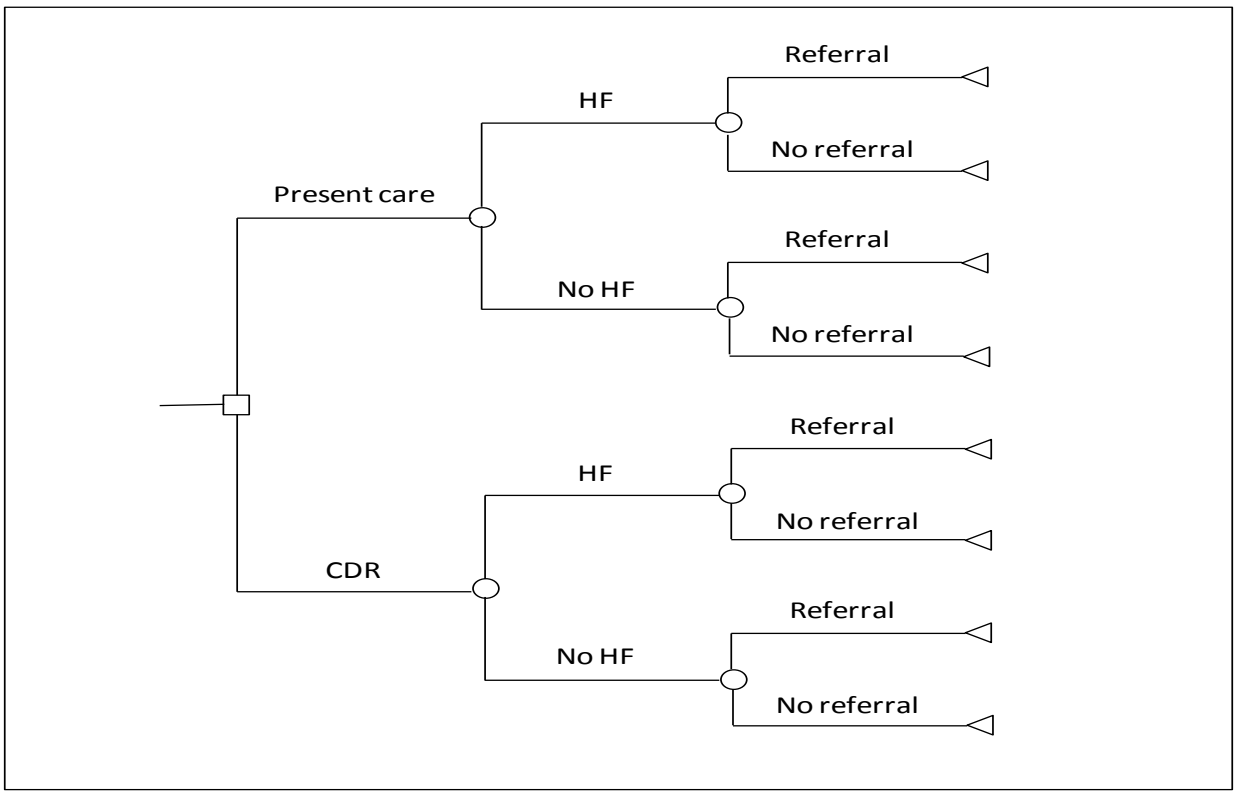

Figure 2. Decision tree used for economic modelling

17.0 DATA MONITORING

17.1. DATA MONITORING

GP performance will be monitored. A record will be kept of contacts made with GPs and recruitment performance monitored throughout the study period. We shall perform a quality assurance check on GP recruitment rates. We shall create an EMIS general practice database query, using appropriate Read Codes to match our inclusion criteria. Practice Managers will run the query every 4-6 weeks to discover if there are any missing patients that would have met inclusion criteria that were not approached by GPs for participation. The quality and completeness of data will be monitored by PC-CRTU and overseen by the study management group.

17.2. DATA MONITORING AND ETHICS COMMITTEE

This is an observational epidemiological study. We shall set up a TSC. Our core research group and study supervision will be established in line with MRC Good Clinical Practice (GCP) guidelines.

17.3. CLINICAL GOVERNANCE ISSUES

To ensure responsibility and accountability for the overall quality of care received by patients during the study period, clinical governance issues concerning all aspects of routine management will be brought to the attention of the study management group and, where applicable, to individual NHS Trusts.

18.0 QUALITY ASSURANCE, ETHICAL CONSIDERATIONS AND CONFIDENTIALITY

18.1. QUALITY ASSURANCE

A data manager will oversee all data collection with built in validation and regular reports to ensure the integrity of data and the database monitored exclusively by the data manager and the statistician. The project manager will ensure that the conduct of the study complies with the currently approved protocol, with the principles of GCP and the NHS Research Governance Framework, and all applicable R&D regulatory procedures.

18.2. ETHICAL CONSIDERATIONS

The main ethical issues associated with this research are patient confidentiality, ensuring that participation in the research does not lead to inferior care, and health and safety issues, outlined below. The study will be conducted in compliance with MRC GCP guidelines and ethical and research governance approval has been sought and granted via the appropriate committees prior to the study start date. Participant information leaflets have been developed with input from service users.

In line with GPC guidelines, we shall ensure that participation in our study does not lead to inferior medical care by performing the diagnostic assessments within 7 days of GP referral and

by informing the patient's GP of the clinical assessment results and any clinical abnormalities uncovered. Therefore, study patients are receiving a higher standard of care than would be likely in routine practice. Post-study medical care will be provided by patients' GPs.

Our institution complies fully with local health and safety standards, including cross-infection safeguards and appropriate handling of human tissue. All relevant research team members have received training in this regard and will adhere to relevant departmental and PC-CRTU Standard Operating Procedures.

18.3. ETHICAL APPROVAL

The study has been submitted to and approved by a Main Research Ethics Committee (09/H1207/121).

18.4. CONFIDENTALITY

We shall establish research procedures to maintain confidentiality of patient information by password-protecting computer files and storing paper records in a locked cabinet with patient identifiable information stored separately. Data will be securely stored in the locked cabinet that cannot be accessed by unauthorised persons. Participants will be assigned a unique study number to preserve anonymity. Only the PI and Data Manager (PC-CRTU) will have access to the coding sheet linking the unique study number to personally-identifiable data on paper records. Only the research nurse and the data manager will have access to personally-identifiable data. A unique study number will be used on all subsequent study documentation to preserve anonymity.

18.5. DATA PROTECTION

All study investigators shall comply with UK Data Protection legislation, with particular attention given to the emphasis on privacy and on processing of personal data extending to disposal or destruction and disclosure to a third party. Data processing and linkage of personal information will be subject to the strictest ethical safeguards of anonymity.

18.6. ARCHIVING

At the end of the study, in line with GCP guidelines, data will be securely archived for a minimum of 15 years at the University. Where a patient has withdrawn consent for their data to be used, they will be confidentially destroyed.

18.7. STUDY REGISTRATION

The study is registered with the UK Clinical Research Network (UKCRN No: 7944); the Central England Primary Care Research Network. The study will obtain ISRCTN registration prior to patient enrolment.

19.0 STATEMENT OF IDEMNITY AND SPONSORSHIP

The University of Oxford has arrangements in place to provide for negligent and non-negligent harm arising from participation in the study for which the University is the Research Sponsor. NHS indemnity operates in respect of the clinical treatment which is provided.

University of Oxford will act as sponsor.

20.0 STUDY ORGANISATIONAL STRUCTURE

20.1. RESPONSIBILITIES

The Chief Investigator is responsible for the design, study set-up, management, and reporting of the study. The Chief Investigator is responsible for ensuring that the clinical management of patients is conducted in accordance with the study protocol, including assessment of eligibility, informed consent and patient safety. The PC-CRTU has overall responsibility for the conduct of the study in accordance with the Research Governance Framework and PC-CRTU SOPs. All co-investigators are responsible for ensuring that regulatory approval has been obtained prior to the start of the study.

20.2. OPERATIONAL STRUCTURE

20.2.1. STUDY MANAGEMENT GROUP

The study management group (PI, co-applicants, independent adviser from PC-CRTU and an internal research active clinician not linked to the study, research team members and service user representatives) will meet monthly and will oversee the study to monitor its conduct, smooth running and progress in accordance with MRC GCP guidelines. Data monitoring, quality assurance and statistical analysis will be performed in accordance with GCP by PC-CRTU staff and overseen by the study management group. Clear lines of responsibility for project management, timescales, recruitment, protocol compliance, statistical analysis and safety will be established. Observers from the EME Board will be invited to all study management group meetings and copies of meeting minutes sent to them.

Two service users actively participated in developing the protocol and patient information documents, and are enthusiastic about the study. The result of this involvement is that the language used in the documentation is free of jargon, acceptable and relevant to patients who will use the materials. We shall form a PPI reference group, ½ invited from public members who have been involved in generic research with the investigators and ½ invited by advert. They will comment on study documentation/research outputs and select two members to serve on the study management group. The PI and project manager will support two service users to attend and actively participate in study management group meetings. This is to enable their active partnership in study management and progress monitoring. We plan to integrate patient involvement in all stages of the study and through further consultation with a wider audience of patients will offer a genuine rather than tokenistic partnership with patients that is critical to ensuring that the evidence generated and service recommendations will be underpinned by the patient voice. Service users will be reimbursed at nationally agreed rates, as recommended by INVOLVE.

20.2.2. PRIMARY CARE CLINICAL TRIALS UNIT

The PC-CRTU will oversee study set-up and monitoring of study conduct according to PC-CRTU SOPs, including providing database development, data verification and statistical analysis.

20.3. FUNDING

The study is funded by the Medical Research Council (MRC) Efficacy & Mechanism Evaluation (EME) programme, with a contribution from the National Institute of Health Research (NIHR), School for Primary Care Research.

21.0 PROJECT TIMETABLE AND MILESTONES

We have already sought and been granted Ethical (09/H1207/121) and R&D approvals. The study has been adopted by the UKCRN (No: 7944) and the general practices have been recruited. The study will be conducted over 36 months: 6 months study set-up, including training GPs in informed consent procedures and protocol compliance; 18 months for patient recruitment and data collection, then 6 and 12 month medical note review and quality of life questionnaires for use in our health economic analysis. We have allowed 9 months for data cleaning, data analysis and write up, including lay summary, EME report and dissemination.

22.0 PUBLICATION POLICY AND DISSEMINATION

Recommended practice in journal guidelines will be followed in relation to authorship. We shall comply with authorship guidelines suggested by the International Committee of Medical Journal Editors, available at http://www.icmje.org.

The results of the study will be published in appropriate peer reviewed journals and the findings presented at national and international conferences. A summary of the findings in a final report will be sent to study participants.

23.0 AUTHORSHIP AND ACKNOWLEDGEMENT

Lynda Tait, Richard Hobbs and Jonathan Mant conceived of and designed the study. Team members (RI, MD) and co-investigators contributed elements to the study design. LT was responsible for drafting the protocol and obtaining advice from a Patient Representative (service user) on the suitability of aims, study procedures and materials. Andrea Roalfe (Statistician) is responsible for the statistical analysis plan. Pelham Barton (Health Economics) is responsible for the economic modelling plan. Richard Hobbs is responsible for the final draft of the protocol.

24.0 NIHR EFFICACY & MECHANISM EVALUATION PROGRAMME REQUIREMENTS

In accordance with NIHR EME programme requirements, EME will be notified in advance of all published work related to the study throughout the course of the research. One draft copy of a proposed publication shall be sent to EME at the same time as submission for publication or at least 28 days before the date intended for publication, whichever is earlier.

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