NIHR HTA Programme

01 October 2012

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HOT Trial

Does Home Oxygen Therapy (HOT) in Addition to Standard Care Reduce Disease Severity and Improve Symptoms in Patients with Chronic Heart Failure?

Protocol

Version 6.0

7th August 2012

University of Hull
Hull and East Yorkshire NHS Trust
Department of Health Sciences, University of York

THE UNIVERSITY of York

CHE
Centre For Health Economics

Hull and East Yorkshire Hospitals NHS
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HOT, Protocol Version 5.0 dated 22.02.2012

Approved by:

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1. Trial Synopsis

Patients with Chronic Heart Failure (CHF) commonly have significant limiting symptoms despite optimal management. The prevalence and clinical relevance of hypoxaemia in patients with CHF is incompletely understood. Currently, Home Oxygen Therapy (HOT), in various forms, is used commonly despite the absence of evidence of benefit.

The present study seeks to address the uncertainties surrounding home oxygen therapy for patients with chronic heart failure who are still severely symptomatic despite maximally tolerated medical therapy. The study will randomise 450 patients equally to its active treatment arms. These are (a) best medical therapy without oxygen (b) best medical therapy with daytime Long Term Oxygen Therapy (LTOT for at least 15 hours per day in the home, including overnight hours) or (c) best medical therapy with Nocturnal Oxygen Therapy (NOT overnight in the home). Each patient will remain within the study for at least 1 year. All patients will continue active treatment within the study until the last patient recruited has completed their 1 year's active treatment, meaning that the first patient recruited will remain on active treatment for approximately 2 years in total. Patients can withdraw at any point, and such incidences will be included within the quality of life analysis.

Primary Research Question

Is there a quality of life benefit from home oxygen therapy given as either long term daytime or nocturnal oxygen therapy compared with best medical therapy in patients with stable severely symptomatic chronic heart failure?

Primary Objectives

- To assess the quality of life benefits of home oxygen therapy in the management of patients with stable CHF who are still severely symptomatic despite maximally tolerated medical therapy.

Secondary Objectives

- To assess the prevalence of hypoxaemia in patients with NYHA III/IV symptoms and optimal medical therapy in order to answer the questions: (a) do patients with stable CHF have arterial hypoxaemia? (b) if so, is this when awake or asleep? and (c) what are its clinical correlates?
- To assess the effect of home oxygen therapy (HOT), delivered as either NOT or LTOT, on symptoms, and disease severity in patients with CHF
- To assess the cost-effectiveness of HOT
- To assess the acceptability to patients and carers of HOT.

Eligibility

The eligibility criteria are as follows:

Inclusion Criteria

- Provided written informed consent and able to complete patient assessments.
- Aged 18 years or over.

Patients with/who are/have:

- Heart failure from any aetiology.
- Heart failure grade NYHA III/IV with left ventricular (LV) systolic dysfunction confirmed by echocardiography. The left ventricular ejection fraction must be less than 40% or graded as at least "moderately" impaired on visual inspection if an accurate ejection fraction cannot be calculated.
- Receiving maximally tolerated medical management of their heart failure
    - Reached target dose (or be on maximally tolerated dose of, or be intolerant of) an inhibitor of the renin angiotensin system shown to improve prognosis
    - Reached target dose (or be on maximally tolerated dose of, or be intolerant of) a beta adrenoceptor antagonist shown to improve prognosis
    - Reached target dose (or be on maximally tolerated dose of, or be intolerant of) an aldosterone antagonist

Exclusion Criteria

Patients who:

- Are unable to provide written informed consent.
- Have had a CRT device implanted within the previous 3 months
- Have co-existing malignant disease if this would affect the study in the investigators' opinion.
- With interstitial lung disease
- Have COPD likely to fulfil criteria for LTOT; FEV1/FVC <70% and FEV1<40% predicted and hypoxia (pO_2 <7.3kPa or saturations <90%)
- Are using any device or medication that would impede their ability to use LTOT or NOT, such as CPAP
- Are unwilling or unable to comply with safety regulations regarding oxygen use, particularly smoking
- Are unable to complete patient related information on entry.

2. Background and Rationale

The standard medical therapy of diuretics for fluid retention and angiotensin converting enzyme inhibitors (ACE-I) or angiotensin-II blockers (A2B) together with beta-blockade (if tolerated) and aldosterone antagonism has resulted in major improvements in mortality and morbidity for patients with chronic heart failure (CHF).[1] However, many patients live for many years with a considerable symptom burden. Breathlessness and fatigue are the two major symptoms and help form the basis of the clinical classification of heart failure severity; the New York Heart Association (NYHA) class of symptoms. Indeed, the presence of symptoms is part of the definition of the heart failure syndrome.

Oxygen therapy is an established part of the management of acute pulmonary oedema complicating heart failure, but its place is less clear in patients with stable compensated CHF. Whilst patients with acute pulmonary oedema undoubtedly have hypoxaemia (low blood oxygen), there are conflicting reports from patients with CHF; whilst some report mild degrees of hypoxaemia, others report that patients with CHF have normal or even higher than normal levels of arterial oxygen.[2 3 4 5 6 7]

A complicating issue is that of sleep disordered breathing (SDB), which appears to be common in patients with CHF.[8] SDB is commonly due to *obstructive* sleep apnoea (OSA) in which collapse of the upper airways during sleep results in obstruction to airflow and hypoxia and arousal. It is typically seen in overweight middle-aged men. In patients with CHF, SDB is commonly *central sleep apnoea* (CSA) and results in a cyclical breathing pattern between episodes of apnoea (and thus hypoxaemia) and over-breathing, sometimes accompanied by arousal. CSA is more common in patients with CHF than in those without. It is associated with disturbed sleep, daytime sleepiness and risk of arrhythmia. However, the contemporary prevalence is unclear; previous studies were done before current medication was routinely used, and case series reports have since suggested that optimisation of medical therapy, selected use of devices (such as resynchronisation) and transplantation reduces CSA.[9 10 11]

Home oxygen therapy (HOT), an expensive treatment which is potentially burdensome for patients and carers, is often prescribed for patients with chronic heart failure, although it is unknown whether it is of benefit in the medium to long-term with regard to symptoms, severity of CHF, hospitalisation or survival. Also unknown, assuming oxygen is of benefit, is how it should be administered; short burst oxygen therapy (SBOT), nocturnal (NOT) or long-term (LTOT). In addition to the concern that there is no proven benefit from oxygen, some reports suggest that hyperoxia leads to clinically significant adverse haemodynamic effects such as increased vascular resistance, left ventricular filling pressure, blood pressure and reduced cardiac output due to the formation of oxygen free radicals.[12]

There are only a few, small, unpowered studies looking at the effect of short term SBOT on breathlessness and exercise tolerance in a variety of conditions. Those trials that randomised patients did not confirm benefit.[13] A large observational study of patients with breathlessness of varying aetiology concluded that oxygen therapy was of no benefit for symptom relief in the absence of hypoxaemia,[14] a finding echoed in a Cochrane review.[15] A recent double blind placebo controlled study confirmed that oxygen was no better than placebo for the relief of intractable breathlessness in study participants, a few of whom had CHF.[16]

The benefits for mortality and morbidity of LTOT in patients with chronic obstructive pulmonary disease and hypoxia are well established,[17] but dependent upon good compliance. One study has suggested that there is less than 30% compliance with prescribed therapy.[18] LTOT (>15 hours per day) has not been studied in patients with left ventricular dysfunction or CHF. The criteria which should be used to assess suitability of LTOT in patients with CHF, let alone benefit in terms of survival, severity of disease or symptomatology is unknown. It is also unknown whether CHF patients would tolerate the intervention which would be more intrusive than NOT alone.

NOT has been studied in small randomised trials in patients with CHF with a maximum follow-up of 3 months[19] [20] [21] [22] [23] and appears to reduce CSA and nocturnal sympathetic activity; evidence of improvement either of cardiac function or symptoms is inconsistent.

3. Aims and Objectives

The aim of the study is to determine if the addition of home oxygen therapy (given either during the day or night) improves life quality for patients with stable, severely symptomatic chronic heart failure, who are already receiving best medical therapy.

3.1 Primary Research Question

- Is there a quality of life benefit from home oxygen therapy given as either long term or nocturnal oxygen therapy compared with best medical therapy in patients with stable severely symptomatic chronic heart failure?

3.2 Primary Objectives

- To assess the quality of life benefits of home oxygen therapy in the management of patients with stable CHF who are still severely symptomatic despite maximally tolerated medical therapy. That is, do patients with chronic heart failure (CHF), with or without hypoxaemia, benefit from home oxygen therapy (HOT), given as Nocturnal Oxygen Therapy (NOT) or Long Term Oxygen Therapy during the day (LTOT)?

3.3 Primary Endpoint

- Effect of different oxygen therapies (LTOT, NOT or no oxygen therapy) on quality of life as measured by change in the Minnesota Living with Heart Failure (MLWHF) score at one year.

3.4 Secondary Objectives

- To assess the prevalence of hypoxaemia in patients with NYHA III/IV symptoms and optimal medical therapy in order to answer the questions: (a) do patients with stable CHF have arterial hypoxaemia? (b) if so, is this when awake or asleep? and (c) what are its clinical correlates?
- To assess the effect of home oxygen therapy (HOT), delivered as either NOT or LTOT, on symptoms, and disease severity in patients with CHF
- To assess the cost-effectiveness of HOT
- To assess the acceptability of HOT to patients and carers

3.5 Secondary Endpoints

1. Mortality
2. Number of days alive and out of hospital
3. Symptomatic status measured by
    a. Health-related quality of life as measured by the Euroqol 5D instrument (EQ-5D)
    b. Severity of and distress caused by breathlessness as measured by the Numerical Rating Scale (NRS) for breathlessness (average and worse over past 24 hours and global change in breathlessness)
    c. Patient satisfaction measured by NRS (in addition to interviews as part of qualitative study)
    d. Epworth Sleepiness score to assess daytime somnolence
    e. Mood using the HAD score
4. Severity of heart failure assessed by
    a. Severity of left ventricular dysfunction on echocardiogram
    b. Nt-proBNP
5. Exercise capacity assessed by
    a. Karnofsky performance scale of physical activity
    b. 6 minute walk test
6. Prevalence of hypoxia measured as
    a. Resting hypoxia
    b. Hypoxia during 6 minute walk test
    c. Nocturnal oxygen saturation and presence of SDB
7. Number of hours of oxygen used measured by concentrator meter.
8. Co-morbidity measured by the Charlson co-morbidity index
9. Cost-effectiveness

4. Study Design

4.1 Design

This is a phase 3, prospective, multi-centre, randomized, parallel-group, controlled trial in patients with stable NYHA Grade III/IV heart failure receiving optimal medical therapy. 450 eligible patients will be allocated by block randomisation 1:1:1 to one of the three limbs of the study, to receive for a period of at least one year, either (a) best medical therapy without home oxygen treatment; (b) best medical therapy with Long Term home Oxygen Therapy (daytime LTOT, for at least 15 hours per day); or (c) nocturnal oxygen therapy (NOT, at least 8 hours per night).

Although the primary end-point of the study is one-year quality of life, data are also to be collected at 3 months during a home visit by the study nurse in order to detect any transient change in quality of life that is lost later. All patients will be asked to continue in the trial with 6-monthly assessments until the last patient recruited has finished one year's participation in the trial. This allows the trial to address quality of life changes and cost effectiveness (the primary outcome), and also to make a provisional assessment of the effect on clinical outcomes, and associated cost effectiveness.

HOT Trial Summary Flow Chart

Patient identification from database, heart failure nurse case list, or treating physician

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Eligibility Criteria Fulfilled

↓

Informed Consent

↓

Baseline Data Collection

↓

Simple Randomisation to one of 3 Groups

↓

Medical Therapy | Medical Therapy + NOT | Medical Therapy + LTOT

↓

Assessments at Baseline, 3 months & 6 monthly thereafter for 1 year, or until the last patient has completed, up to a maximum of 2 years.

↓

Study End with Assessment of Patient for Further NHS Oxygen Therapy

There will be a nested, qualitative, single centre sub-study involving semi-structured interviews with a purposive sample of patients in each arm of the study to explore the views and experience of participants and their carers regarding oxygen therapy. An entirely separate, single centre sub-study will assess the acute effect of oxygen on haemodynamics in patients with CHF.

4.2 Problems of a Placebo Controlled Study

The investigators considered including a 'placebo' sham oxygen concentrator arm in order to tease out a 'quality of life' placebo effect associated with the presence of a concentrator. The sham concentrator would deliver normal room air instead of air with increased concentration of oxygen, This approach, however, suffers from analytical and practical problems.

Analytically, it is difficult to separate the extent of any change in symptoms because there will be a combination of potential effects from the oxygen therapy itself and the effect associated with prolonged use of nasal cannulae and concentrators, complicating comparison across the trial arms. In other words, it would not be possible to detect what proportion of any quality of life impact is due to the placebo effect of the device, versus the intrusive effect of the nasal cannulae. Hence, the investigators decided on an open label design to allow comparison with a group of patients treated with best medical therapy.

Secondly, the act of using the concentrator may be beneficial by increasing air flow across the face: by stimulating the upper airway receptors, it may thereby alleviate the symptoms of breathlessness.[24] The sham treatment may thus have a 'true', clinically demonstrable, beneficial effect, further complicating comparison.

Finally, motivated patients could easily unblind the study (for example, by holding a smoldering match near the concentrator to see if it re-ignited), and would have plentiful opportunity to do so, since the concentrators are in their homes. Crucially, for the trial, it would be very difficult to know whether individual patients had unblinded the study.

Practically, there are several financial, legal, regulatory and logistical problems associated with the use of a placebo machine. The use of 'sham devices' requires the manufacture of specially modified and marked devices, to sit alongside similarly marked standard devices within separate storage facilities, managed under separate legal contracts, and requiring regulatory approval at both national and local Trust levels. This dramatically increases the costs and complexity of delivering the trial, while reducing our ability to recruit patients from different centres, and increasing delays. The research team has spent some 18 months attempting to overcome these hurdles.

For these reasons, the investigators have decided to opt for an open three-armed treatment trial: any effect of the intervention will thus be a "real world" estimate of any benefit from oxygen therapy, including an estimate of any placebo effect.

4.3: Problems of Stratification by Hypoxaemia.

The research team have considered stratification by hypoxia, but have rejected it on the advice of both the HTA monitors and the Trial Steering Committee. The true prevalence of hypoxaemia in patients with chronic heart failure is not known, but from the available evidence, the investigators suspect that it is very low. However, it is certainly possible that some patients have minor degrees of hypoxaemia (in the range of 92 – 96%) and may benefit; it is also likely that patients have hypoxaemia overnight.

Given that home oxygen therapy is commonly prescribed for heart failure patients on the basis of symptoms rather than on the basis of hypoxaemia, the investigators did not want to risk limiting recruitment by insisting on a qualification based on an arbitrary level of hypoxaemia. The researchers will, however, analyse the data based on pre-treatment hypoxaemia.

4.4 Trial Timeline

Setup - 3 months (1 April 2011 – 30 June 2011)

IRAS approvals (MREC & CSP)
Completion of any additional licensing & approvals
Start 3 & 6 monthly TMG, TSC & DMEC cycles
Update and establish trial materials & database
Train centre teams
Start of systematic health economic review
Development of preliminary cost-effectiveness model

Recruitment - 12 months (1 July 2011 – 30 June 2012)

Commence patient recruitment and data collection
Monitor and support patient recruitment and retention
Launch and complete Qualitative & Oxygen sub studies

Follow Up - 24 months (ends 30 June 2013)

Maintain data collection at centres.
Address data problems that arise to avoid delays to subsequent stages.
Analyse and present initial Qualitative and Oxygen sub study findings.

Data Cleaning - 3 months (1 July – 30 September 2013)

Analysis - 3 months (1 October 2013 – 31 December 2013)

Write Up of Trial Report - 3 months (1 January – 31 March 2013)

Submission of HTA Draft Report – 14 days (15 April 2014)

Publish findings for the Main study, Qualitative and Oxygen sub studies.

5. Patient Eligibility and Participation

5.1 Patient Numbers and Identification

Four hundred and fifty (450) patients will be recruited into the study over a period of 1 year. Participating centres have large cohorts of eligible patients, who are already receiving long term CHF care, supporting the screening of case lists. Patients may also be detected incidentally, though specific heart failure, general cardiology or general clinics, or through inpatient admissions. It is anticipated that the bulk of patients will be identified through clinic-based case-finding of existing patient cohorts.

It is anticipated that the trial will recruit froma large number of centres, over a period of one year, with each centre expected to recruit at least 10 patients.

The symptom burden and prognostic impact of the illness are high in patients with severe symptoms, and such patients have potentially the most to gain from oxygen therapy if it is beneficial. Patients can continue oxygen treatment at the end of the trial if they have found it beneficial.

5.2 Eligibility Criteria

5.2.1 Inclusion Criteria

- Provided written informed consent and able to complete patient assessments.
- Aged 18 years or over.

Patients with/who are/have:

- Heart failure from any aetiology.
- Heart failure grade NYHA III/IV with left ventricular (LV) systolic dysfunction confirmed by echocardiography. The left ventricular ejection fraction must be less than 40% or graded as at least "moderately" impaired on visual inspection if an accurate ejection fraction cannot be calculated.
- Receiving maximally tolerated medical management of their heart failure
    - Reached target dose (or be on maximally tolerated dose of, or be intolerant of) an inhibitor of the renin angiotensin system shown to improve prognosis
    - Reached target dose (or be on maximally tolerated dose of, or be intolerant of) a beta adrenoceptor antagonist shown to improve prognosis
    - Reached target dose (or be on maximally tolerated dose of, or be intolerant of) an aldosterone antagonist

5.2.2 Exclusion Criteria

Patients who:

- Are unable to provide written informed consent.
- Have had a CRT device implanted within the previous 3 months
- Have co-existing malignant disease if this would affect the study in the investigators' opinion.
- Patients with persistent basal pulmonary crackles found to have interstitial lung disease
- Have COPD likely to fulfil criteria for LTOT; FEV1/FVC <70% and FEV1<40% predicted and hypoxia (pO_2 <7.3kPa or saturations <90%)
- Are using any device or medication that would impede their ability to use LTOT or NOT, such as CPAP
- Unwilling or unable to comply with safety regulations regarding oxygen use, particularly smoking
- Are unable to complete patient related information on entry.

5.3 Entry Procedures

Eligible patients will be approached in CHF, cardiology or general medical clinics. Patients may also be identified through eligible patient lists held at NHS GP practices (Patient Identification Centres), or via existing lists of likely eligible patients held within NHS Hospitals, and introduced to the trial by letter. They will be introduced to the study by a member of the local clinical or research team, usually the clinician responsible for their treatment (usually a consultant cardiologist), and have the opportunity to discuss the trial fully with both the clinician and the research nurse. Each participant will be informed of the aims, methods, anticipated benefits, potential hazards and discomforts of the study, both through the Patient Information Sheet (PIS) and verbally. The participant's right not to participate and the right to withdraw at any time, without the need to give an explanation and without detriment to their overall treatment will be clearly stated. Patients will have at least 24 hours between

receiving the Patient Information Sheet (PIS) and giving their informed consent. Confirmation of the written informed consent may then be taken by clinicians or suitably qualified nurses according to local practice.

Transport will be provided for patients, or transport costs paid according to preference. Patients will be recruited and followed up through the existing routine ongoing 6 monthly clinics. Most of the clinical assessments are routine, meaning the patient would undergo them whether they were in the trial or not. The three month assessments will normally be carried out in the participant's home, depending on patient preference. The final data collection (at the completion of the trial) will use the existing patient notes, so will not require a clinic or home visit.

All consent forms will be stored in accordance with local requirements and copies given to the participant, entered into the patient's hospital notes and kept in the site study file. Patient entry will be logged on-line with the York Trials Unit, who will allocate the patients trial number and also the arm to which they are randomised.

5.4 Data Management

All data will be completely anonymised for purposes of analysis and any subsequent reports or publications. For the purposes of ongoing data management, individuals will only be identified by trial numbers, patient initials and date of birth. All study data will be recorded on case report forms (CRFs) that York Trials Unit will provide to all participating centres. York Trials Unit will collect, monitor, and record data.

5.5 Discontinuation and Withdrawal

Patient participation in the trial will be discontinued if –

- the patient withdraws consent
- the patient opts to discontinue participation
- the patients is withdrawn from the trial by the treating physician or medical researcher

If patients wish their entire data set to be withdrawn from the trial, they may notify the local research team, or the York Trials Unit.

5.6 Trial Completion

The trial will complete after the last patient has completed their final clinic assessment. This should occur 27 months after trial launch, and 24 months after the first patient is recruited. Participants will also have the opportunity to request continuation of HOT if they found this beneficial. Otherwise, HOT will be removed from the patient's home by the local oxygen supplier.

6. Trial Evaluations

6.1 Patient Pathway

After giving consent and completing baseline assessments, patients will be randomized to receive either (a) best medical treatment, without home oxygen, or (b) best medical treatment with daytime oxygen delivered in their home, or (c) best medical treatment with nighttime oxygen delivered in their home. In the event that the local clinical team feels the patients requires assessment for Obstructive Sleep Apnoea, the patient will not be randomised until a clinical decision is made. If the patient is treated using CPAP, or another technique that would impede their ability to use LTOT or NOT, then they will not be randomised. If they are not treated, they will be randomsied, provided that this is within 1 month of the baseline assessment being completed. If the patient is randomized to receive home oxygen therapy (HOT), a clinical prescription will be completed and sent to the local oxygen supply company holding the standard NHS contract within that particular region. Arrangements will be made locally between the patient and the local oxygen supplier to install the oxygen concentrators in the patient's home.

HOT is administered by home oxygen concentrators. Concentrators will be delivered to the patient's home by the recruiting hospital's usual oxygen supplier, in accordance with existing NHS agreements. These concentrators filter room air, concentrate the oxygen levels, and deliver the oxygen-enriched air to the patient. Installation will typically occur within 3 days from receipt of the prescription by the oxygen supply company.

CHF patients usually attend clinic every 6 months, and clinic data would be collected at these routine clinic appointments In this way, patients will not be unduly burdened with additional hospital visits. At the conclusion of the trial, final clinical data will be collected using existing hospital records, including admission and mortality. The types of data collected at each point are summarised in Table 1, and explained below. At the conclusion of an individual patient's trial participation, HOT concentrators will be removed from their home unless they wish to continue treatment.

6.2 Quality of Life Questionnaires & Assessments

The quality of life assessments undertaken are:

- Minnesota Living with Heart Failure questionnaire (MLWHF)

This is a validated, disease specific, QoL instrument widely used in heart failure research both to assess symptoms severity and response to treatment.[25] [26] It is the primary endpoint measure for the present study. It consists of 21 questions focussing on the impact of heart failure on QoL. Patients are asked to rate the extent to which their heart failure has prevented them from living as they wanted during the last month using questions rated on a scale of 0 (no effect) to 5 (very much). The questionnaire is scored by summating the responses to all 21 questions; thus resulting in a score from 0 to 105 with a higher score reflecting poorer quality of life. The MLWHF validated Quality of Life (QoL) score version 2 is easy to complete and has been shown to be especially effective in older patients with co-morbidities.[27]

- The EuroQoL EQ-5D

This is a self-administered, validated, measure of health status and consists of a 5-question multi-attribute questionnaire and a visual analogue self-rating scale.[28] [29] Respondents are asked to rate severity of their current problems (level 1= no problems, level 2 = some/moderate problems, level 3 = severe/ extreme problems) for five dimensions of health: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Patients can be classified into 243 (3^5) health states plus two further additional states (unconscious and dead).

- Epworth Sleep Score

The Epworth is a standard scale for screening for, and assessing the severity of, sleep disordered breathing.

- Breathlessness Numerical Rating Scale

This measures average and worst breathlessness and distress due to breathlessness over the past 24 hours (anchored with “not breathless” and “worst breathlessness imaginable”).[30] It is highly correlated with VAS scores and more repeatable.[31] It will also used to assess patients satisfaction with oxygen treatment (anchored with “not at all satisfied” to “very satisfied”).

- Hospital Anxiety and Depression Scale

The HAD score is a well validated screening tool for depression and anxiety and easy to complete.[32]

6.3 Clinical Assessments

The clinical assessments undertaken are:

- Age, sex, aetiology of heart failure, current medication

- Spirometry

To determine forced vital capacity and forced expiratory volume in the first second. Baseline assessments can use measures taken within the last 3 months. Subsequent assessments can use measures taken within the last month.

- Standard blood biochemistry and full blood count.
- All assessments can use measures taken within the last month.

- Standard examination to record:

(a) resting pulse rate and blood pressure, (b) severity of peripheral oedema (if any), (c) severity of lung crackles (if any), (d) weight, (e) height

- 12 lead ECG

To determine cardiac rhythm and ECG intervals

- Echocardiogram

Routine echocardiographic assessment will be performed including M-mode, 2D images, and colour flow Doppler recordings. Measurements will be taken in accordance with American Echocardiography Society/European Association of Echocardiography guidelines.[33] [34] Echocardiography will be carried out by trained operators. LV systolic function will be assessed by attempted measurement of LVEF using Simpson's biplane method in all subjects, and in all subjects by estimation on a scale of normal–mild–mild-to-moderate–moderate–moderate-to-severe–severe systolic impairment. Baseline assessments can use measures taken within the last 3 months. Subsequent assessments can use measures taken within the last month.

- 6 minute walk test
- The 6-minute walk test (6-MWT) will follow a standardized protocol.[35] [36] [37] A flat, obstacle-free corridor, with chairs placed at either end will be used. Patients will be instructed to walk as far as possible, turning 180º every 15 m in the allotted time of six minutes. During the 6-MWT, patients will be able to rest, if needed, and time remaining will be called every second minute. Patients will walk unaccompanied so as not to influence walking speed. After six minutes, patients will be instructed to stop and total distance covered will be calculated to the nearest metre. Standardised verbal encouragement will be given to patients after 2 min and 4 min. All assessments can use measures taken within the last month.

- N-terminal proBNP (B-type Natriuretic Peptide) measurement
- Nt-pro BNP blood samples can be processed in the local laboratory, using standard systems or point of care testing, according to local practice. Centres should ensure that they use the same assay type on a patient while the patient is within the trial. All assessments can use measures taken within the last month.

- Assessment of arterial oxygenation
    - Any standard sleep monitoring system can be used for the home recording of nocturnal polysomnography including arterial oxygen saturation, and to assess the presence of Sleep Disordered Breathing.Arterial saturation by pulse oximetry at baseline and at the completion of the 6 minute walk test
    - Overnight oximetry to record
        - Nadir of oxygenation overnight
        - Proportion of night time spent with oxygen saturation below 95%

Sleep study tests are a preferred, but not essential, part of the trial protocol. Use of automated reporting is permissible if the tests are undertaken.

- Assessment of NYHA Grade
    - Class I – no symptoms
    - Class II – breathless and/or fatigue on moderate exertion
    - Class III – breathless and/or fatigue on mild exertion
    - Class IV – breathless and/or fatigue at rest

6.4 Performance Measurements

- Charlson Co-morbidity Index[38]

This is a validated age-comorbidity index used to estimate relative risk of death from prognostic clinical covariates, and useful in studies with 1 to 2 year follow up.

- Karnofsky Performance Status Scale[39 40]

This validated scale incorporates the components of physical activity, work and self care of patients.

6.5 Health Economic Assessments

In addition to the EQ5D

- Health Service Use Questionnaire

The Health Service Use Questionnaire is designed to measure the level of health service resource use. Respondents are asked to recall the amount of use they have made of the specified services over the previous 6 months.

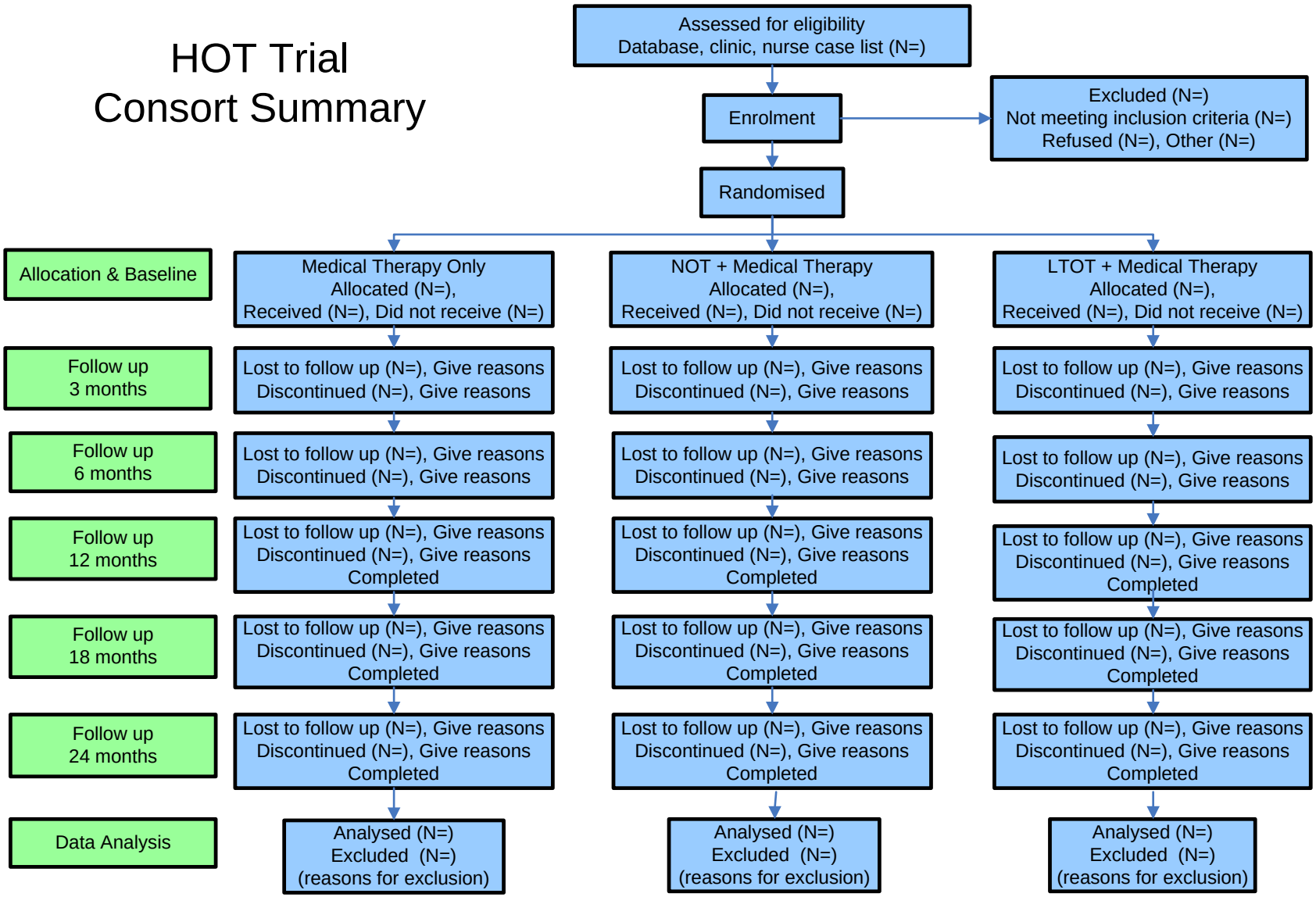
Table 1: HOT Main Trial – Patient Assessment Schedule

Assessment	Months After Recruitment[1]					
	Baseline	**3**	**6**	**12**	**18**	**24**
Clinical	**Clinic**	**Home**	**Clinic**	**Clinic**	**Clinic**	**Clinic**
Age, Sex, Aetiology, Height	X					
Weight	X		X	X	X	X
Current Medication	X	**X**	X	X	X	X
Resting Pulse Rate & Blood Pressure, Respiratory Rate	X	**X**	X	X	X	X
Assessment of Peripheral Oedema & Lung Crackles	X		X	X	X	X
ECG	X		X	X	X	X
Blood Test - BCP, FBC (Standard Biochem' & Haem')	X		X	X	X	X
Blood Test – Nt pro BNP	**X**[2]	**X**	**X**	**X**	**X**	**X**
Spirometry	X			X		X
Echocardiogram	X			**X**		**X**
6 Minute Walk Test & Pre/Post O2 Saturation	X		**X**	**X**	**X**	**X**
Overnight Sleep Test (if locally accessible)	**X**		**X**	**X**	**X**	**X**
Charlson Co-Morbidity Index	**X**		**X**	**X**	**X**	**X**
Karnofsky Performance Score	**X**	**X**	**X**	**X**	**X**	**X**
Quality of Life						
Minnesota Living with Heart Failure Questionnaire (MLWHF)	**X**	**X**	**X**	**X**	**X**	**X**
Numerical Rating Scale - Breathlessness (NRS)	**X**	**X**	**X**	**X**	**X**	**X**
Hospital Anxiety & Depression Scale (HADS)	**X**		**X**	**X**	**X**	**X**
Epworth Sleep Score	**X**	**X**	**X**	**X**	**X**	**X**
Health Economics						
EuroQoL	**X**		**X**	**X**	**X**	**X**
Health Service Use Questionnaire (not all questions)	**X**		**X**	**X**	**X**	**X**

[1] It is intended that all patients will participate in the trial for 12 months, or until the last patient has completed, up to a maximum of 24 months. Assessments occur at 3 months (+/- 7 days), or at 6 monthly time points (+/- 14 days) thereafter. At trial end summary data on mortality and hospitalisations will be collected from clinical records for all participants.

[2] Investigations in 'blue' are trial investigations. Those in 'black' are routinely used within clinics for this patient group.

HOT Trial
Consort Summary



7. Economic Analysis and Modelling

Systematic reviews will be conducted to identify existing studies providing information on the costs, resource use and health outcomes associated with CHF and HOT. The analysis will be undertaken from the cost perspective of the NHS and using methods outlined in the National Institute of Health and Clinical Excellence (NICE) methods guide.[xli]

The cost-effectiveness results will be expressed in terms of the incremental health service costs and quality adjusted life years (QALYs) gained. Where appropriate, separate analyses will be conducted for patient sub-groups with different levels of baseline risk or expected benefit. The primary analysis will be the cost per QALY gained over one year of treatment with NOT or LTOT relative to best medical therapy.

To explore more long-term outcomes a probabilistic decision-analytic model will be constructed to represent the natural history of CHF with which the cost-effectiveness of NOT and LTOT can be evaluated relative each other and to best medical therapy over a longer time horizon.[xlii] The model will track the resource use and costs as well as the quality of life and health outcomes for patients with CHF. Prognostic information collected during the trial will be used in combination with published studies to link changes in severity of disease at one year to long term outcomes. Structural and modelling uncertainty will be fully explored using scenario analysis. The decision-analytic model will follow the guidelines for good modelling practice.[xliii]

8. Statistical Considerations

8.1 Sample Size

Study power is difficult to calculate. The Minnesota Living with Heart Failure scale is the most widespread tool for assessing quality of life in patients with chronic heart failure. An improvement of 5 is sometimes taken to be a minimum clinically important difference,[xliv] but others have suggested that a change of one standard error around the mean score is needed (around 6 or 7, depending upon the population studied).[xlv] There are no studies of long term oxygen therapy to help guide us. The MIRALCE trial of biventricular pacing was powered for a 13 point improvement in MLWHF, and found a difference of 9 between treatment groups.[xlvi] The CARE-HF study of biventricular pacing found an improvement of 10.6 with intervention.[xlvii] In the absence of hard data on which to base study size, we have taken a Minnesota score of 10 as an arbitrary indicator of the minimum improvement necessary to justify the cost and inconvenience of oxygen therapy for patients.

For a 10 point difference in MLWHF score, and with a standard deviation of 25 and assuming a P of 0.025 (for two comparisons) and 80% power we will need 119 in each group or 150 in each group if we assume a 20% attrition rate.

8.2 Statistical Analysis

The clinical trial will be reported according to the CONSORT guidelines for clinical trials. Baseline data (sex, age, diagnosis distributions etc.) will be presented in tabular form. Data will be summarised using descriptive statistics. Data will be analysed according to intention-to-treat criteria. A secondary analysis will be an on-treatment analysis. A secondary analysis will be by baseline mean nocturnal oxygen saturation. Whilst patients may, of course, withdraw from treatment at any time, they will all be encouraged to remain under follow up.

Statistical comparisons will compare the measurements of primary and secondary outcomes between the groups. For continuous data, ANCOVA will be used to compare the groups, whilst controlling for the baseline measure and confounding factors. KM and Cox regression will be used for time to event data such as mortality. All analyses will be undertaken on SPSS.

Missing data is a well recognised problem in longitudinal studies, particularly with patients with advanced disease. We will handle missing data by using the extreme values. By making the assumption that the missing value is the worst it could be for the intervention and the best it could be for the standard care group (best medical therapy). If there remains a statistically significant difference between treatments then one can be sure that the results are robust. Other techniques that we have considered involve building a regression equation to predict the value of the missing data from the baseline characteristics from patients with no missing values or the use of other imputation techniques such as mean values. Expert statistical advice will be provided by Dr Victoria Allgar.

9. Pharmacovigilance

The collection and reporting of data on adverse events and serious adverse events will be in accordance with ICH GCP and the Research Governance Framework 2005.

9.1 Definitions

Adverse Event (AE)

An adverse event (AE) is any untoward medical occurrence in a patient which does not necessarily have a causal relationship with the study treatments or procedures. An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with a treatment or procedure, whether or not considered related.

Adverse Reaction (AR)

All noxious and unintended responses related to a study treatment or procedure should be considered adverse drug reactions.

Serious Adverse Event (SAE)

Any untoward medical occurrence in a patient that

(a) Results in death
(b) Is life-threatening
(c) Requires hospitalisation or prolongation of existing hospitalisation
(d) Results in persistent or significant disability or incapacity
(e) Consists of a congenital anomaly or birth defect
(f) Is otherwise considered to be medically significant by the investigator e.g. intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation.

The term “life-threatening” 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.

Hospitalisations planned prior to enrolment in the trial or for social reasons should not normally be considered as SAEs unless the hospitalisation has to be prolonged.

Suspected Unexpected Serious Adverse Reaction (SUSAR)

A suspected unexpected serious adverse reaction (SUSAR) is an adverse reaction that is classified as serious and it is suspected that it is caused by a study treatment or procedure.

Severity

The term severity is used to describe the intensity of an adverse event and should not be confused with seriousness which is based on the patient/event outcome or action criteria.

9.2 Adverse Event (AE) Reporting

An adverse event (AE) is any untoward medical occurrence in a patient who is taking part in a research study. In this trial, a pre-existing condition (i.e., a disorder present before the AE reporting period started and noted on the pre-treatment medical history/physical examination form/medical notes) is not to be reported as an AE unless the condition worsens or episodes increase in frequency during the AE-reporting period.

Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, are not to be reported as AEs. However, the medical condition for which the procedure is performed is to be reported if it meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period is to be reported as the AE (serious) and the resulting appendicectomy noted under comments.

If a clinically significant abnormal laboratory value occurs, this abnormality (but not the value itself) should be entered on the adverse event page.

Expected Adverse events include the following:

- Worsening of symptoms of heart failure
- Admission to hospital for acute decompensation of heart failure
- Worsening angina
- Admission to hospital with angina

Each trial subject will be questioned about adverse events at each visit. The investigator will record all directly observed AEs and all AEs spontaneously reported by the trial subject.

The AE reporting period for this trial begins on randomisation, and ends 30 days after the patients' final research clinic appointment.

9.3 Recording and Reporting Instructions

Each AE will be classified by the investigator as SERIOUS or NONSERIOUS and should be recorded on the 'serious adverse event form' or 'non serious adverse event form'.

An adverse event is defined as being serious if it is an untoward occurrence that:

(a) results in death,
(b) is life-threatening,
(c) requires hospitalisation or prolongation of existing hospitalisation,
(d) results in persistent or significant disability or incapacity,
(e) consists of a congenital anomaly or birth defect, or
(f) is otherwise considered medically significant by the investigator

If a research participant experiences an adverse event which in the opinion of the chief investigator is both

- 'related': that is, it resulted from administration of any of the research procedures; and
- 'unexpected': that is, the type of event is not listed in the protocol as an expected occurrence.

Then it will be reported to the Research Ethics Committee that gave a favourable opinion of the study and the sponsor (Hull and East Yorkshire Hospitals NHS Trust R&D department) **within 15 days** of the CI becoming aware of the event using the NRES safety report form available from:

http://www.nres.npsa.nhs.uk/applications/after-ethical-review/safetyreports/safety-reports-for-all-other-research/#safetynonCTIMPrepotingSAEs

9.4 Annual Progress Reports

An annual progress report will be submitted to the main REC which gave the favourable opinion 12 months after the date on which the favourable opinion was given and thereafter until the end of the study according to the NRES website below:

http://www.nres.npsa.nhs.uk/applications/after-ethical-review/annual-progress-reports/

10. Research Governance

The Neon Trial was approved by the HTA for funding on 31 March 2008(HTA Ref 06/80/01), and by the Northern and Yorkshire Multi Centre Research Ethics Committee on 24 August 2009 (Ref: 09/H0903/41).. The trial was substantially revised, renamed 'HOT' and approved by MREC on 18 May 2011. A non substantial amendment addressed minor issues on 15 May 2012.

10.1 Study Organisation Structures & Responsibilities

The sponsor of the trial will be Hull and East Yorkshire NHS Trust. The trial will be managed by the University of York Trials Unit, on behalf of Professor Andrew Clark (Chief Investigator).

Chief Investigator - The Chief Investigator will have overall responsibility for the design, coordination and management of the study. These include:

- Trial authorization including responsibility for the protocol, obtaining approvals from MREC
- Ensuring that the trial is conducted according to Good Clinical Practice (GCP)
- Assessment of SAEs and providing a prompt response as to whether the SAE is a SUSAR.

Trial Manager The trial manager will be directly responsible to the Chief Investigator for liaison between the HTA, Hull and East Yorkshire NHS Trust, York TU, the Hull-York Medical School, the Comprehensive Local Research Networks, local project teams, and other parties as required. Duties include;

- Coordination of the components of the trial
- Initial start up and ongoing assistance with centres
- Financial management
- Reporting

Clinical Trials Unit – The Chief Investigator has delegated the responsibility for overall project management, data management, monitoring and ongoing statistical support to the York TU. Responsibilities include:

- Assistance with completion of the NRES form and communication with MREC
- Production of trial specific documentation (i.e. CRFs)
- Assistance with SSA procedures within centres
- Facilitating set up of trial centres
- Data management
- Responding to centre queries
- Pharmacovigilance – Reporting of SAEs / SUSARs

Statistical Analysis – Dr Victoria Allgar, employed by the Hull-York Medical School, and based within the Department of Health Sciences, University of York, will undertake the final analysis arising from this study.

The Principal Investigator at each participating centre will be responsible for obtaining local site-specific assessment (SSA) approval, and for the local conduct of the study. All correspondence relating to research ethics committees should be filed and maintained by the Investigator at each site.

Local Project Teams – These will consist of consultants, usually **Cardiologists** (responsible for introducing the patient to the trial and ensuring eligibility and consent) and **Research Nurses or other suitably qualified nurses** (responsible for patient recruitment, obtaining consent, and co-ordination of all aspects of data collection). Centres are specifically responsible for conducting the trial in accordance with the protocol, standard operating procedures (SOPs), trial agreement and MRC-GCP of both the trial and local practice.

10.2 Trial Management, Monitoring and Oversight

Data Monitoring and Ethics Committee (DMEC) – The DMEC will normally review the safety and ethics of the trial by reviewing interim data every 6 months. The terms of reference of the Data Monitoring and Ethics Committee are to:

- Ensure that patient considerations are of prime importance.
- To review any safety issues arising during the trial (including any SAEs and SUSARs).
- To report (following each DMEC meeting) its recommendations regarding trial continuation to the Trial Steering Committee.
- To consider any requests for release of interim trial data and to make recommendations to the Trial Steering Committee on the advisability of this.
- Should data summaries be required during the study, to provide to the Trial Steering Committee appropriate information and advice on the data gathered to date that will not jeopardize the integrity of the study.

Trial Steering Committee (TSC) – The TSC will provide overall supervision of the trial, in particular trial progress, adherence to protocol, patient safety and consideration of new information. An independent chair has been appointed and all co-applicants are members. The Committee will normally meet every 6 months. The terms of reference of the Trial Steering Committee are as follows:

- To provide overall supervision of the trial, ensuring adherence to protocol.
- To review developments during the trial and recommend appropriate action.
- To ensure that the rights, safety and well being of trial participants is safeguarded and prioritized.

Trial Management Group (TMG) - The TMG will comprise of the Chief Investigator, other lead investigators (clinical and non-clinical), members with a specific interest (e.g. nurses; patient representatives) and members of York TU. The TMG will be responsible for the day-to-day running and management of the trial and will meet approximately every six months for the duration of the trial. The terms of reference of the Trial Management Group are as follows:

- Be responsible for the day-to-day running of the trial.

- Be responsible for the management of the trial

Data Monitoring
York TU will monitor receipt of CRFs and evaluate incoming CRFs for compliance with the protocol, inconsistencies and missing data. Participating centres may be monitored by York TU to confirm compliance with the protocol and complete source data verification (SDV).

10.3 Centre Approval, Start-up Procedures and Ongoing Support

The following documentation must be received by York TU in order for an institution to be eligible to participate in the HOT Trial:

- Confirmation of a favourable Site Specific Assessment (SSA)
- A copy of local R&D approval
- Completed Investigator Statement, signed by the institution Principal Investigator (PI) on behalf of all staff at the site who will be working on the Home Oxygen study
- Completed Delegation Log and Contact Details
- CV's, including evidence of GCP training for named persons

Once this documentation has been received, confirmation of centre approval will be sent to the local Principal Investigator by the HOT team at the York TU.

Prior to commencing the study, training sessions will be provided to clinical and research teams at centres, defining how the trial is to be managed by the Trial Manager. Phone support, and visit support, will be provided to centres as per their requirements during the course of the study, mainly by the Trial Manager, with the support of the York TU as appropriate.

10.4 Data Management

Each participant will be assigned a study identification number. Case Report Forms (CRFs) will only use the participant's trial identification number and date of birth. Source documents required by the York TU will be fully anonymised. No personal medical data will leave the individual study site. CRFs and records will be stored at York TU in secure facilities with access limited to study staff. All data will be stored at the York TU on a secure and password-protected electronic database.

Key indicators (recruitment rates, refusal rates, completeness of data, drop out, tolerability, adverse events etc) will be recorded on an ongoing basis, to enable quick identification and resolution of difficulties, and also to provide full information for both the TSC and DMEC.

The NHS approved oxygen supply company will provide the trial with readings from the home oxygen equipment, using existing data that is routinely collected.

10.5 Dissemination and Publication Policy

The results will be disseminated in peer reviewed journals, through the local cardiology network and at national and international meetings in both palliative care and cardiology. All publications and presentations relating to the trial are required to be authorized by the Trial Management Group (TMG). Authorship of any publication will always include the Chief Investigator, Statisticians, and senior staff associated with the trial, while further authorship will be determined by centre accrual. Participants may only present data with the permission of the TMG, and this can only be after a period of at least 6 months after the main results are published. Patients participating within the trial will be sent a summary of the findings.

11. Ethics, Confidentiality and Liability

11.1 Ethical Considerations

The patient population under study is a potentially vulnerable group and care should be taken not to introduce further physical, psychological or financial burden with entry into studies. However, this must be balanced with the need to test practices that are potentially beneficial or unhelpful or burdensome. In order to try to address some of these concerns, this study:

- Includes a research team with a broad base of clinical experience including palliative care and psychology and includes a qualitative component to access patient views
- Minimises the need for hospital visits, by employing sufficient research nurses to allow home visits for follow- up
- Uses assessments kept to short form and non-invasive techniques
- Will reimburse reasonable travel costs
- Provides support for participants as part of research nurse role
- Allows continuation of the treatment if perceived to be beneficial to that patient once follow-up has been completed
- It is recognised that some participants will be in a position of clinical dependence with some of the research team as patients under their care. GCP procedures with regard to consent will be observed.

Patients for whom there is a proven clinical indication (such as patients with COPD and hypoxia) are excluded from the trial. Patients randomised to receive oxygen therapy who find it beneficial, can continue on this therapy at the end of the trial period.

11.2 Patient Confidentiality

The patient's full name, date of birth, hospital number and NHS number (Community Health Index and/or hospital number in Scotland or equivalents in Wales and Northern Ireland) will be collected and usable by approved members of the trial team, including the University of York Trials Unit to enable tracing through national records, and the safe management of patients. The personal data recorded on all records will be regarded as confidential, and to preserve each patient's anonymity, only their initials and date of birth will be recorded on CRFs. The patients will be identified within the CRFs by the use of a unique trial number allocated to them upon entry into the study.

The Principal Investigator (or delegate) at each site must keep a log of patients' trial numbers, names, addresses and hospital numbers. The Principal Investigator must ensure that patient confidentiality is maintained and that all trial documents (e.g. consent forms) are maintained in strict confidence.

York CTU will maintain the confidentiality of all patients' data in accordance with The Data Protection Act 1998 and will not reproduce or disclose any information by which patients could be identified, other than the reporting of serious adverse events. Representatives of York CTU will be required to have access to patients' medical records for the purposes of monitoring and source data verification. Confidentiality will be maintained at all times. Representatives of regulatory authorities may require access to patients' medical records for regulatory purposes only.

11.3 Statement of Indemnity

The trial is endorsed by the Health Technology Assessment section of the Department of Health in the UK. Indemnity for participating hospitals is provided by the usual NHS arrangements.

12. The Study Team

The Chief Investigator, Andrew Clark, is based in the Academic Department of Cardiology in the Hull and East Yorkshire NHS Trust. He maintains a database of CHF patients to help patient screening and is well placed to recruit to studies. Hull provides secondary and tertiary cardiology services for a population of 1.5 million patients. Around 2 500 patients with CHF are actively managed by the department and tracked through the departmental database. The department has a national and international reputation for heart failure research. It is the lead centre for several multicentre studies, including CARE-HF, and is recruiting for up to 6 multicentre studies at any one time. Clinical trials managers are employed by the department and are familiar with running multicentre trials. Mike Greenstone is a respiratory physician who leads the tertiary referral service for sleep and home ventilation. He is the regional lead for oxygen services and has regional funding to investigate palliative care needs of patients with COPD. He is the editor and systematic reviewer for the Cochrane Airways Group and has contributed to national guidelines on mesothelioma, asthma and bronchiectasis. He has published in peer reviewed journals on palliative care, COPD, asthma and bronchiectasis.

Miriam Johnson is based at Hull-York Medical School (University of Hull) and has contributed to a systematic review on the use of oxygen in the symptom control of breathlessness. She is PI for a recently completed clinical feasibility trial of non-pharmacological management of breathlessness and about to start the powered subsequent NIHR funded multi-centred study. She is co-investigator (with AC and DT) on a recently completed trial on the use of opioids for breathlessness in patients with CHF. She is Chair-elect of the NCRI breathlessness research sub-group which has international representation. Through this group she has strong collaborative links with the trial investigators of Oxygen-HF, the only other study world-wide of oxygen in heart failure. She has led or worked on trials in the fields of venous thromboembolism in cancer and symptom control. She has developed one of the first joint cardiology/palliative medicine services in the UK. She also has past and current experience collaborating with qualitative researchers in the Department of Psychology at the University of Hull, at Hull/York Medical School and the Department of Health Sciences at the University of York.

Iain Squire is based in the University of Leicester Department of Cardiovascular Sciences. Professor Squire established one of the first heart failure clinical services in the UK, recognised for its excellence. The heart failure clinic serves a population of around 950,000 and offers a one-stop diagnostic service with close links with specialists in echocardiography, coronary revascularisation and cardiac imaging. Dr Squire established the network of heart failure specialist nurses (8 whole time equivalent) serving the entire local population. The specialist nurses make direct referrals to the

heart failure clinic and are integrated with Palliative Care. Professor Squire has an extensive record of research in heart failure, with over 70 peer reviewed publications in the area, including an HTA funded project involving screening in less than 1 year over 1300 individuals for previously undiagnosed LVSD. His Heart Failure Research Group has an international reputation.

Darlington Memorial Hospital provides secondary care cardiology services to South Durham, a population of 250,000. Heart failure clinics, running for 6 years, receive referrals from primary care and ward discharges. From the outset, a patient database has been maintained which will help recruitment. The clinic is staffed by Professor Murphy (Professor of Cardiovascular Medicine at Durham University) and Dr Fuat (Senior Lecturer within the Centre for Integrated Healthcare Studies, Durham University). The cardiology department has a well-established research unit and although other heart failure trials are in progress, none would compete with the proposed study. The PCT employs four heart failure nurses and there are patient support groups.

Leeds hospitals have a national and international reputation for research into heart failure including being the lead centre for the landmark AIRE study. Professor Kearney is the clinical lead for heart failure services at the Leeds Teaching Hospitals, and supervises the multidisciplinary team including senior lecturer, lecturer, senior nurse and pharmacist. He has an extensive track record in research in vascular biology and heart failure. All patients discharged from Leeds cardiologists with a primary diagnosis of CHF are seen by the heart failure team within 2 weeks of discharge. Detailed physiological characterisation is performed and patients entered into a database. This provides an ideal platform to perform clinical research in high risk patients with CHF.

David Torgerson is the Director of the York Trials Unit. He has been an investigator or co-investigator of numerous trials including cardiac rehabilitation. He has extensively published on the methodology of clinical trials, and is an experienced health economist. He also has an interest in the recruitment into RCTs and has recently published a systematic review in this area.

Victoria Allgar, based at Hull-York Medical School (the University of York) leads the HYMS Statistical Consultancy Service, providing a comprehensive statistical support service to NHS professionals in North and East Yorkshire, and northern Lincolnshire. She is a Chartered Statistician with the Royal Statistical Society and has extensively published, usually as the lead statistician.

We have taken advice from two Health Economists who have contributed to the design of the study, including Susan Griffin, a co-applicant. Susan is a senior research fellow at the Centre for Health Economics and has been a health economist for 8 years. She has conducted cost-effectiveness analyses in the areas of sleep apnoea, cardiovascular disease, cancer and HIV.

Ian Harvey has been recruited as Trial Manager. He has been a clinical trial manager for 7 years, and has been responsible for seeing 3 multicentre trials through to completion. Sarah Cockayne is an experienced health sciences researcher and trial coordinator. She has worked at the YTU for eight years and has coordinated five multicentred trials. Sarah was the main applicant on the NIHR - HTA EVerT trial.

Through the British Society for Heart Failure, we have identified additional interested centres that presently have a research interest, and have experience in recruiting patients to clinical trials. We will recruit from a total of 10 centres, thereby reducing the demands on each centre, stabilising the rate of recruitment overall, and reducing the impact of recruitment difficulties at any single centre.

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