Study Title: A retrospective observational analysis of a cohort with Heart Failure with Preserved Ejection Fraction from a BNP pathway clinic

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Sponsor:	Portsmouth Hospitals NHS Trust
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Signatures:	The approved protocol should be signed by author(s) and/or person(s) authorised to sign the protocol

Protocol Development Team: Co-Investigators as listed above, Jamie Sergeant (Biostatistician at University of Manchester) and patient representative team (Sharon Court, Anna Glanville-Hearson, Chris Staples, Joleen Tobias, Noreen Cole, Bill Ware and Darren Jenkinson).

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1. AMENDMENT HISTORY

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

2. SYNOPSIS

Study Title	A retrospective observational analysis of a cohort with Heart Failure with Preserved Ejection Fraction from a BNP pathway clinic
Problem statement	Heart failure with preserved ejection fraction (HFpEF) is a complex condition with various causes that is not yet fully understood. Most significantly there is no single method of diagnosing or treating the condition. Recently a novel non-invasive diagnostic criterion to predict the likelihood of HFpEF was proposed by Reddy et al. (2018) called H2FPEF. The main limitation of this study was the use of a single centre population from the Mayo clinic in Rochester, US. Another limitation is that the H2FPEF diagnostic criterion consists of common and often co-existing conditions which could as a result overestimate HFpEF probability. The aim of the investigators is to retrospectively test the H2FPEF criteria on the population at Queen Alexandra Hospital (QAH) in Portsmouth, which is of a lower socio-economic status and greater ethnic diversity. Implications of the project if H2FPEF is proved to be generalizable to the population is that it can be used within the Trust and rolled out to others. This would allow diagnosis to be made quicker and more cost effectively using echocardiography and without the need for invasive cardiac catheterisation. On the other hand if H2FPEF is found not to be applicable to the population then further research would be required to find the ideal diagnostic tool.
Research question / hypothesis	The investigator's hypothesis is that when H2FPEF criteria is compared against retrospectively held data for the patient population at QAH that this will overestimate the probability of HFpEF
Study Design	The study is a single-centre retrospective observational analysis
Study Participants	Patients who attended heart failure clinics at Queen Alexandra Hospital between January 1st 2016 – December 31st 2016
Planned Sample Size	2000
Follow-up duration	1 year
Planned Study Period	04/10/2019 – 30/04/2020
Primary Objective	The primary objective of the investigator's project is to test if the H2FPEF score accurately predicts HFpEF on the population at Queen Alexandra Hospital.
Secondary Objectives	•Investigate if H2FPEF overestimates HFpEF diagnosis on the patient population when compared against known BNP levels. •To evaluate if H2FPEF can be validated on the patient population and be utilised to improve patient pathway for HFpEF. •To monitor patient responses to treatments and care for one year.
Primary Outcome Measure	To assess the predictive accuracy of H2FPEF at predicting HFpEF on the patient population as calculated by logistic regression, with diagnostic accuracy being assessed by sensitivity and specificity calculations.
Secondary Outcome Measures	• ANOVA will be performed to provide one simultaneous evaluation of the data to determine if there is a significant difference between

	H2FPEF score and diagnosis of HFpEF. •To assess number of hospital admissions and any changes in treatment/ care after one year for the population.

3. ABBREVIATIONS

List all abbreviations / acronyms in alphabetical order, for example:

AF	Atrial Fibrillation
ANOVA	Analysis of Variance
BMI	Body Mass Index
BNP	B-type natriuretic peptide
BSE	British Society of Echocardiography
ECG	12 lead Electrocardiogram
E/e'	Echocardiographic measure of ventricular filling pressures
EF	Ejection Fraction
GCP	Good Clinical Practise
H2FPEF	New diagnostic criteria for HFpEF (Heavy, ≥2 Hypertensive medications, atrial fibrillation, pulmonary hypertension, elderly, elevated filling pressure
HFmrEF	Heart Failure with Mid-Range Ejection Fraction
HFpEF	Heart Failure with Preserved Ejection Fraction
HFrEF	Heart Failure with Reduced Ejection Fraction
LV	Left Ventricle
NHS	National Health Service
NIHR	National Institute for Health Research
NT-proBNP	N-Terminal pro-B-type Naturetic Peptide
PASP	Pulmonary Artery Systolic Pressure
PPI	Patient Public Involvement
QAH	Queen Alexandra Hospital
STP	Scientist Training Programme

4.   LAY SUMMARY

Heart failure with preserved ejection fraction (HFpEF) is a complex condition with various causes that is not yet fully understood. Heart failure is a long-term condition where the heart is unable to pump enough blood to meet the demands of the body. Heart failure is then categorised based on ejection fraction, which is the percentage of how much blood the heart pumps out each beat. HFpEF is a form of heart failure were the heart still pumps >50% of its volume each heart beat. Most significantly there is no method of diagnosing or treating the condition. A recent project proposed non-invasive criteria using routinely collected data to predict the likelihood of HFpEF. This was termed H2FPEF and uses: weight, number of hypertensive medications prescribed, age, presence of atrial fibrillation, ventricular filling pressures and pulmonary hypertension. The main limitation of this study is the use of a single centre population from the Mayo clinic in Rochester, US. Another limitation is that the H2FPEF criterion consists of common conditions which could as a result overestimate HFpEF probability. The aim of the investigators is to test the H2FPEF criteria on previous data already held from heart failure clinic database at Queen Alexandra Hospital (QAH) in Portsmouth. Implications of the project if H2FPEF is proved to be accurate on the population is that it can be used within the Trust and other trusts. This would allow HFpEF to be identified quicker at a reduced cost for the trust and reduced risk for the patient avoiding invasive investigations. On the other hand if H2FPEF is found not to be applicable to the population then further research would be required to find the ideal tool or method to identify HFpEF. A follow-up of patients is also proposed to monitor any long-term outcomes and how they respond to treatments.

5.   BACKGROUND AND RATIONALE

Epidemiology:

In the UK heart failure is the biggest cause of hospital admissions in people aged over 65, and is associated with poor morbidity and mortality outcomes if not managed effectively (National Institute for Health Care and Excellence [NICE], 2015). Heart failure is a complex heterogeneous condition characterised by typical symptoms and signs indicative of structural or functional cardiac abnormalities which despite normal filling pressures results in failure to deliver oxygen at a rate proportionate to the demands of metabolizing tissues (Ponikowski et al., 2016). Typical symptoms of heart failure include shortness of breath, reduced exercise tolerance, fatigue, orthopnoea and paroxysmal nocturnal dyspnoea; with signs such as peripheral oedema, functional mitral regurgitation, murmur and elevated jugular venous pressure (Allen et al., 2015). All of these signs and symptoms are however not specific to heart failure and could be caused by alternative conditions which makes diagnosis difficult (Oren and Goldberg, 2017).

Heart failure is categorised based on ejection fraction (EF);
•   EF <40% - Heart failure with reduced ejection fraction (HFrEF)
•   EF 40-49% - Heart failure with mid-range ejection fraction (HFmrEF)
•   EF ≥50% - Heart failure with preserved ejection fraction (HFpEF)

The aetiology of HFpEF is less well understood compared to HFrEF because it is not a uniform disease and patients usually have a combination of morbidities, but there is now a greater focus on it as it is just as prevalent (Lam et al., 2011; Dunlay et al., 2017; van Empel and Rocca, 2018). No effective therapies have as yet been found for management of HFpEF, with therapies that have proven effective in reducing mortality and morbidity in HFrEF patients not having the same effect for HFpEF patients, making this an important research focus (O'Gallagher and Shah, 2018). Approximately half of heart failure patients are now believed to have HFpEF, with the prevalence increasing and set to become the dominant form of heart failure as the condition becomes better understood and diagnosed (Banerjee, 2016; Deaton et al., 2018).

Background:

HFpEF was previously characterised as 'diastolic dysfunction' but this terminology was changed as it was found that diastolic dysfunction was also seen in patients with 'systolic dysfunction' (Borlaug and Paulus, 2011). Myocardial stiffness which leads to increased filling pressures is a common pathophysiologic attribute of HFpEF despite its multifactorial aetiology (Telles and Marwick, 2018). Other common conditions associated with HFpEF include: atrial fibrillation (AF), chronotropic incompetence, pulmonary hypertension, right ventricular dysfunction and endothelial dysfunction; with common non-specific risk factors such as: age, gender, hypertension, obesity, diabetes, metabolic syndrome and renal failure (Borlaug, 2014; Ferrari et al., 2015; Harper et al., 2018). This complex heterogeneity of HFpEF which is not yet fully understood highlights the difficulty that clinicians have in being able to diagnose the condition.

Diagnosis of HFpEF is difficult and as of yet there is no test to confirm diagnosis, with current guidelines saying initial diagnosis should include the presence of typical signs and symptoms, an elevated B-type natriuretic peptide (BNP) (>35 pg/mL and/or N-Terminal pro-

B-type Natriuretic Peptide [NT-proBNP] >125 pg/mL) and ejection fraction ≥50% (Lekavich et al., 2015; Ponikowski et al., 2016). Echocardiography is the preferred method of assessing for HFpEF due to it being widely available, non-invasive, and able to provide immediate results (Ponikowski et al., 2016). Recent studies comparing the use of echocardiography against 'gold standard' invasive cardiac catheterisation to assess cardiac filling pressures found echocardiography to be just as accurate and reliable (Anderson et al., 2017; Lancellotti et al., 2017). Implications of this research would be that patients could be assessed as outpatients by focus echocardiography rather than invasively in the cardiac catheterisation lab, which would improve patient experience, enhance patient outcomes and prove cost-effective for trusts.

In response Reddy et al (2018) recently proposed non-invasive diagnostic criteria called H2FPEF which assesses patients based on body mass index (BMI), the number of hypertensive medications they take, presence of AF, pulmonary pressure, age and filling pressure. The advantage of the H2FPEF score is that it uses only non-invasive echocardiography data alongside routine clinical data making it easy to derive. However one key limitation of their study is the population they used was all from the Mayo clinic and so the generalisability of their results has not been tested for other populations, such as those of lower socioeconomic status like in Portsmouth. A further limitation is the parameters chosen to create H2FPEF are all relatively common morbidities and usually co-exist, making it likely that it will over diagnose HFpEF.

Research questions:

The main research question the investigators are investigating is whether the H2FPEF criteria proposed by Reddy et al. (2018) is an accurate predictor of HFpEF on the patient population at QAH. In the original paper by Reddy et al. (2018) they created and tested H2FPEF criteria on their study population from the Mayo clinic, Rochester, US. This population is predominantly Caucasian and of a high socioeconomic status and so lacks generalisability. In response the investigators are testing the H2FPEF criteria on the population at QAH which is of a lower socioeconomic status, to investigate if it remains an accurate predictor of HFpEF.

Risks:

As the investigators study is a retrospective observational study there are no risks to participants, and all data obtained will be anonymised with no personally identifiable data being analysed.

Impact:

The main outcome of this project will be whether the H2FPEF score is able to accurately predict HFpEF on the patient population of QAH, Portsmouth or if it overestimates diagnosis. If the investigator's research hypothesis is accepted then future research will be required to either optimise H2FPEF score or to develop new HFpEF diagnostic criteria. The enigma of HFpEF would continue to be the focus of research with the aim of developing an applicable clinical diagnostic tool. Alternatively if the investigators accept the null hypothesis then the H2FPEF score will have been validated on the population and would have the potential to be used by QAH and other trusts. Future research would then be required on other populations to further assess the generalisability of H2FPEF. The implications of this would be that patients are able to be diagnosed with HFpEF quicker and non-invasively requiring just an ECG, a focus echocardiogram and a routine clinical examination. Consequently invasive

cardiac catheterisation would not be required for diagnosis which would improve patient outcomes and patient service experience, as well as being cost-effective for the trust.

6. PRELIMINARY STUDIES

This is the first study undertaken in response to the recent study by Reddy et al. (2018).

7. AIMS AND OBJECTIVES

7.1 Primary Objective

The primary objective of the investigator's project is to test if the H2FPEF score proposed by Reddy et al (2018) accurately predicts HFpEF on the population at QAH, Portsmouth.

7.2 Secondary Objectives

The investigator's secondary objectives are to:

• Investigate if H2FPEF overestimates HFpEF diagnosis on the patient population when compared against known BNP levels.
• To evaluate if H2FPEF can be validated on the patient population and be utilised to improve patient pathway for HFpEF.
• Follow patients up over one year to monitor outcomes

8. STUDY DESIGN

8.1 Summary of Study Design

Data will be collected retrospectively from consecutive patients who meet the inclusion criteria to calculate a H2FPEF score: weight, number of hypertensive medications prescribed, presence of AF or not, presence of pulmonary hypertension or not, age and filling pressure. A total H2FPEF score will then be calculated for each patient as per Reddy et al. (2018) protocol: BMI > 30 kg/m2 (2 points), ≥2 anti-hypertensive medications (1 point), paroxysmal or permanent AF (3 points), pulmonary artery systolic pressure >35mmHg (1 point), age >60 years (1 point), E/e' filling pressure > 9 (1 point).

8.2 Primary and Secondary Outcome Measures

Primary outcome measure

- Accuracy of H2FPEF at predicting HFpEF on the patient population will be assessed as specificity and sensitivity as calculated by logistic regression

Secondary outcome measure

- Investigate if H2FPEF overestimates HFpEF diagnosis on the patient population when compared against known BNP levels.
- To evaluate if H2FPEF can be validated on the patient population and be utilised to improve patient pathway for HFpEF.
- To assess patient outcomes after one year, including any changes in medication or treatment as well as number of hospital admissions and reported symptoms.

9.   STUDY PARTICIPANTS

9.1   Study Setting

Participants will have attended a heart failure clinic with a cardiology consultant at QAH between 01/01/2016-31/12/2016.

9.2   Overall Description of Study Participants

All participants will be patients who have attended heart failure clinics at QAH between 01/01/2016 – 31/12/2016. Eligibility will be met by the inclusion and exclusion criteria.

9.3   Eligibility Criteria

Inclusion Criteria

The participant must meet ALL of the following criteria to be considered eligible for the study:

- Age 18-85yrs inclusive
- Currently or previously attended a heart failure clinic with a cardiology consultant at QAH
- Had an echocardiogram, ECG, BNP blood biomarker test in addition to a routine clinical evaluation (including age, weight and number of hypertensive medications) during January 1st 2016 – December 31st 2016.

Exclusion Criteria

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

- Known structural heart disease
- Significant heart valve disease (greater than mild stenosis, greater than moderate regurgitation)
- Pulmonary arterial hypertension
- Constrictive pericarditis
- Pre-existing cardiomyopathy
- Heart transplantation

10.   SAMPLING

All eligible participants between 01/01/2016 – 31/12/2016 will be included in the study. This is to allow sufficient time to be able to follow patient outcomes up. Outcomes such as any changes to medication and treatment as well as any hospital admissions and reported symptoms will be assessed. Including patients from 2016 will allow us to assess these outcomes one year after their clinic appointment.

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11. STUDY PROCEDURES

All data collection will be performed retrospectively. All data will be obtained from the heart failure clinic database. One year follow-up to assess patient outcomes will also be performed retrospectively where data is available.

11.1 Recruitment

Data will be collected retrospectively from eligible participants with data already held on the heart failure clinic database. A member of the patient's direct clinical care team will identify the participants who meet the eligibility criteria for data extraction.

All data obtained will be anonymised with no patient identifiable data being recorded as part of the initial part of the study. A separate pseudonymised document including patient hospital number only will recorded to allow clinical outcome data to be obtained for the follow-up study.

11.2 Screening and Enrolment

The heart failure clinic database will be screened during the study dates for eligible participants. Any eligible participants will then be included in the study, with only the relevant clinical data being recorded. Patients will be anonymised, with a separate document detailing pseudonymisation. No personally identifiable data will be included in the analysis or results.

11.3 Randomisation

N/A

11.4 Study Assessments

All data will be collected retrospectively from the heart failure clinic database at QAH. Data will be collected on: weight, number of hypertensive medications prescribed, presence of AF or not, presence of pulmonary hypertension or not, age and filling pressure. These are the factors that make up Reddy et al. (2018) H2FPEF score. In addition the patient's ejection fraction and BNP will also be recorded as a measure to determine HFpEF diagnosis. All data will be anonymised and recorded on a Microsoft Excel spreadsheet, with a separate document documenting the pseudonymised data. All data will have been routinely collected as part of the heart failure patient pathway:

- Echocardiography - A non-invasive ultrasound test which takes approximately 30 minutes and has no radiation risk. Echocardiogram results will be used to ascertain pulmonary pressure and diastolic filling pressure. This will have been performed routinely as part of the heart failure patient pathway at QAH. All scans will have been performed on GE Healthcare Vivid echocardiography machines by a trained sonographer from the Cardiac Investigations Unit at QAH. A standard operating procedure exists for performing echocardiogram. In accordance with local practice personal protective equipment is worn for this test. ECG electrodes and ultrasound gel can be a potential risk to the patient with regards to dermatological reaction/sensitivity, however both are hypoallergenic substances.

- 12-lead electrocardiogram (ECG) - A non-invasive test of the electrical conduction of the heart assessing heart rate and rhythm. ECG results will be used to determine if the patient is in AF or not. All ECG will have been recorded with the use of the hospitals standard machine (MAC 1200, GE Healthcare). All tests will have been

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performed by trained staff within the Cardiac Investigations Unit at QAH. Standard operating procedures are followed to perform ECG. ECG will have been performed routinely as part of the heart failure patient pathway at QAH.

- Weight - Using a standard trust scale (Marsden Weighing Company, UK)
- Age and Number of hypertensive medications taken - Assessed from patient records

12. DATA HANDLING AND RECORD KEEPING

12.1 Data Collection Forms

All data will be collected and stored electronically using the following format.

Participant ID	BMI (>30Kg/m^2) Yes/No	≥2 anti-hypertensive medications Yes/No	AF Yes/No	PASP >35mmHg Yes/No	Age (>60 years) Yes/No	E/e' (>9) Yes/No	H2FPEF Score	Patient Outcomes

12.2 Data Management

Data management will be conducted by the investigators using clinical, access databases and excel documents. All study data obtained will be documented electronically on a Microsoft Excel document on a personal Trust drive at the investigator site and will be accessible only by the research team. Data will be monitored at the investigator site. The participants will be identified by a study specific participants number and/or code in any database. The name and any other identifying detail will not be included in any study data electronic file.

13. DATA ANALYSIS

13.1 Description of Analysis Populations

All eligible participants will be analysed the same as per protocol.

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13.2   Analysis of Outcome Measures

To determine if the H2FPEF score was accurate in predicting HFpEF the calculated H2FPEF score will be compared against BNP blood test results using the cut-off points stated by the European Society of Cardiology (Ponikowski et al., 2016). To test our hypothesis an analysis of variance test (ANOVA) will be performed to provide one simultaneous evaluation of the data to determine if there is a significant difference between H2FPEF score and diagnosis of HFpEF. A logistic regression analysis will then be carried out to give an odds ratio and provide a predictive analysis of the data. All statistical analysis will be performed using SPSS software.

13.3   Procedure for Dealing with Missing, Unused and Spurious Data

Only data relating to the H2FPEF score will be collected; as per inclusion/ exclusion criteria no patient will be included in the study unless they had all of the necessary tests at their clinic visit. If no data is available for one year follow-up then the patient will be excluded from this assessment, but will still be included in the initial assessment of the H2FPEF diagnostic criterion.

13.4   Procedures for Reporting any Deviation(s) from the Original Statistical Analysis Plan

If any queries regarding statistical analysis are raised by any of the study team then a consultation with a qualified statistician will be undertook to find a suitable solution that all members are satisfied with.

13.5   Interim analysis and criteria for early study termination
N/A

14.   ETHICS

The main ethical issue associated with the investigator's study design is due to the retrospective nature of the data collection meaning that consent is unable to be obtained. However, all data is already stored on the heart failure clinic database at QAH from when they will have attended, with all tests being performed routinely as part of their clinical patient pathway. In addition no personally identifiable data will be used during analysis or results of the study. Patients will be anonymised during the initial data collection, with a separate document detailing pseudonymisation using patient hospital number only.

14.1   Participant Confidentiality

The study staff will ensure that the participants' anonymity is maintained. Only the relevant clinical data will be collected, and will only be accessed by members of the research team that are involved in the clinical care and would have access anyway. All documents will be stored securely on secured personal hospital drives with password protection and only accessible by study staff and authorised personnel. The study will comply with the Data Protection Act which requires data to be anonymised as soon as it is practical to do so.

14.2   Other Ethical Considerations
N/A

14.3   Declaration of Helsinki

Where appropriate the study protocol will be carried out in accordance with the Declaration of Helsinki: No unnecessary suffering will be caused to participants and the benefits of the study

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outweigh any risks.

14.4 ICH Guidelines for Good Clinical Practice

All staff involved in the study will be GCP trained as per NIHR and will be monitored by the sponsor to ensure adherence to GCP.

15. PATIENT PUBLIC INVOLVEMENT (PPI)

15.1 Study design

This proposal originated from clinicians, with the proposal being presented to the PPI team at QAH for review. Review from PPI team was positive with agreement of the research background and requirement, as well as retrospective study design. Lay people will not be participating in data collection or analysis, but will be included as part of the ethical review panel and forming of lay summaries.

15.2 Study implementation

Public and patient involvement will be considered before data collection begins. Patient Research Ambassadors have been presented with and discussed to give their input and advice.
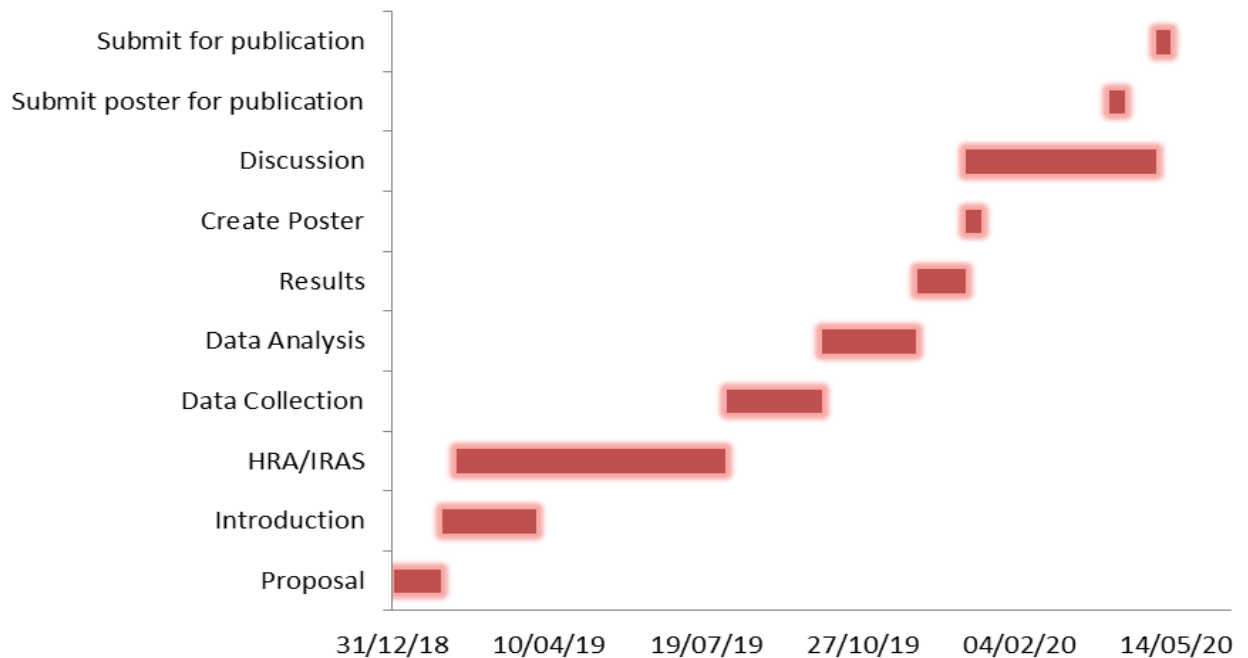
15.3 Dissemination

Initial study write-up will be submitted to Manchester Metropolitan University to satisfy the major project module of the primary investigators MSc programme. Results of the study will be presented at local and national conferences, as well as being submitted for journal publication. Patient Research Ambassadors will be invited for advice on areas for public dissemination of results.

16. FINANCING AND INSURANCE

This study is funded through The Scientist Training Programme (STP) as part of Mr Paul Evans's Clinical Scientist training. Portsmouth Hospitals NHS Trust will be the sponsor of this study.

17. TIMETABLE AND ORGANISATIONAL CHART

18. RESOURCES, EQUIPMENT AND PHYSICAL FACILITIES

All of the study protocol will be carried out on a Portsmouth Hospitals NHS Trust computer at QAH

19. DISSEMINATION AND OUTCOME

Initial study write-up will be submitted to Manchester Metropolitan University to satisfy the major project module of the primary investigators MSc programme. Applications will be made to present study results at local level at Portsmouth Hospitals NHS Trust Healthcare Scientist conferences, as well as national conferences such as BSE. Final write-up of the study will also be submitted for journal publication.

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