PhD Project Brief - Using new low dose CT cardiac imaging techniques to help define pre-operative risk of silent MI in surgery

1. Background to the study

Coronary heart disease is the UK's single biggest killer. There are nearly 2.3 million people living with coronary heart disease in the UK. Nearly one in six men and more than one in ten women die from coronary artery disease (CAD). The cost of premature death, lost productivity, hospital treatment and prescriptions is estimated at £19 billion (1). Coronary heart disease typically presents in one of two ways. Gradual narrowing of the arteries reduces blood flow to the heart resulting in extertional chest pain (angina). Alternatively, atheromatous plaques can rupture into the vessel lumen causing acute narrowing or occlusion of a vessel which results in cell death (myocardial infarction) or arrythmia (typically sudden death due to ventricular fibrillation). The later usually occurs in plaques causing little or no luminal narrowing, thus patients are usually asymptomatic. The latter group account for approximately 50% of presentations.

Patients undergoing surgery are at risk of major peri-operative cardiac events (cardiac death, non-fatal myocardial infarction (MI) and non-fatal cardiac arrest). Surgery causes increased stress on the heart and increases the coaguability of the blood. Plaque rupture is therefore more likely in the peri-operative period. A recent study of 15,000 patients demonstrated 8% had significant cardiac muscle damage (demonstrated by raised blood enzymes) and this was associated with a 3.9x greater mortality [2]. Patients experiencing a full blown MI after non-cardiac surgery have a hospital mortality rate of 15%–25%, which is an independent risk factor for cardiovascular death during the 6 months following surgery. Patients who have a cardiac arrest after non-cardiac surgery have a hospital mortality rate of 65%, and non-fatal perioperative cardiac arrest is a risk factor for cardiac death during the 5 years following surgery.

There is clearly a need to identify patients who are at high risk of cardiac events preoperatively so effective informed consent, prognostication and risk modification can occur. Current preoperative assessment seeks to identify "high risk" patients. Consensus guidelines categorize patients into risk groups for cardiac complications using demographics, co morbidities, functional capacity and planned operation as discriminators. However, current methods discriminate only moderately well between patients at high versus low risk.

Computed Tomography (CT) is an imaging technique where an x-ray source is rotated around the patient (typically in a spiral fashion) and measurements are made of the number of x-rays which are stopped by the patient's organs by associated detectors. This information is then converted to anatomical images. It is one of the main modalities in imaging. All patients with suspected cancer will undergo such a scan to look for spread of their disease. In this type of scan no assessment of the coronary arteries can be made as cardiac movement blurs them.

Cardiac Computed Tomographic Angiography (CTCA) is a reliable non-invasive method to investigate CAD (3). This technique is similar to standard CT but the scanner is linked to the patient's heart via an ECG. This allows extraction of CT data when the heart is relatively stationary. The scanning technique typically demands a much finer spiral to obtain information about the whole of the cardiac cycle. Many more rotations around the patient result in a higher radiation exposure and necessitate it being done as a separate scan. Using CTCA in the pre-operative patient has been shown not only to be effective in both demonstrating CAD, but also demonstration of this disease is useful in preoperative risk assessment and superior to conventional techniques (4).

Recent advances in CT technology have made it possible to perform cardiac CT using a new technique (called prospective axial scanning). Such scanning only requires a small part of the cardiac cycle to obtain images. This technique has been shown to be as accurate as a spiral CTCA in selected patients. This technique is more dose efficient and is typically less radiation then a standard CT scan (as used for assessing patients with suspected cancer). As all patients with suspected cancer undergo a scan of their chest using this new technique it may be possible to obtain this important information about the coronary arteries in all patients without significant additional procedures, intravenous contrast or radiation – i.e. an opportunistic CTCA without any penalty.

However, such a technique has not been performed before and so there is no information on its accuracy. Two important pieces of information are required:

1. Is it possible to obtain diagnostic images of the coronary arteries using this new technique in this patient population?

2. Does performing CT of the chest with the new technique effect image quality (and therefore diagnostic accuracy) for the structures outside the heart? If it reduces image quality of these structures then clearly its applicability would be limited.

These key questions will form the basis of the project. Assessment of the potential role of the new technique requires the following stages:

A. Systematic reviews of pre-operative risk assessment -to establish what is known.
B. A feasibility study where patients receive both the conventional (spiral scan) and the new (axial scan) gated scan and subjective and objective comparison is made between the two to ensure non-inferiority for non-cardiac structures and accessibility of cardiac structures.
C. The role of the new technique in pre-operative risk assessment and identification of high risk patients compared to conventional techniques will be developed during the PhD. Through Dr Mintos study we will see if CTCA can be used as a gate keeper for patients requiring cardiopulmonary stress testing (i.e. is a normal CTCA predictive of a normal exercise test?).

2. Problem or issue to be investigated.

CTCA techniques have been developed using a new technique that allows scans to be performed at similar doses to routine scans. These are normally done just to evaluate the heart. Such scans could be performed as part of routine practice in patients undergoing staging scans for cancer to reveal information pre-operatively about CAD. This study will evaluate in this population whether it possible to evaluate the coronaries. It will also demonstrate that the image quality is comparable to conventional scanning for non-cardiac structures.

3. Aims and Objectives

Aims:

To improve the prediction of risk of cardiac events in patients about to undergo major operations and so improve patients outcomes

Objectives:

- To systematically review the best current methods of predicting cardiac risk
- To assess the feasibility of prospective axial cardiac CT scans
- To make a direct comparison between the spiral scans and the prospective axial scans objectively and subjectively for image quality.
- To assess the number of coronary artery segments in each patient that can be seen and are assessable in this patient population.
- To evaluate the addition in predictive risk likely to flow from use of prospective axial cardiac CT scans

4. Proposed methodology

4.1. The systematic review

Systematic Review Methods

The key methodology will be based upon the principles of systematic review outlined by the developing Cochrane Diagnostic Test Accuracy Handbook. The method section of the project is divided into three main sections: criteria for study inclusion, search method for identification of studies, and data collection and analysis. A full protocol for publication and prospective registration on PROSPERO will be developed by the candidate advised by the supervisory team before proceeding. The key features listed below anticipate that test accuracy studies will be the main included studies. Prognosis studies may also be helpful, so we will extend the methods if this is the case, drawing on the advice of the Cochrane Prognosis Methods Working Group.

Criteria for considering studies for this review

Studies comparing index test to a reference standard in patients with pre-operative cardiovascular risk factors verified by established techniques will be eligible for inclusion. All referred patients with potential pre-operative cardiovascular risk factors are considered, provided the cases are confirmed by appropriately timed index test and reference standard. The considered index test is computed tomography (CT) coronary angiogram or calcium scoring on CT. The target condition is recognised cardiovascular risk factors that have the potential of leading to adverse outcomes during the post-operative period. The authors' own definitions of the target condition and positive index tests will be accepted. Previous cardiac events, for example, an old myocardial infarct, and a positive result yielded from a combination of established tests, including serum cholesterol, electrocardiogram (ECG), exercise tolerance test, cardiac magnetic resonance, and myocardial perfusion scan, are accepted as the reference standard test. A

stand-alone significant positive result from one of the described techniques will also be accepted. If a composite ending is used by studies, only those with a sufficient duration of follow-up will be accepted.

Search methods for identification of studies

The applicant will work closely with the Trial Search Coordinator in PenTAG, University of Exeter, in selecting sources to search, and developing and running search strategies. PubMed will be searched as the primary source for existing reviews. The references of identified studies and of important review articles will be scrutinised for possible studies missed by electronic searches. Finally a number of key authors will be contacted requesting other studies. Professor Carl Roobottom, an expert of CT coronary angiogram, will performed hand searching of key cardiovascular and radiology journals, including The New England Journal of Medicine and Radiology, and conference abstracts to identify relevant studies.

Data collection and analysis

After the completion of the stages above, the applicant will screen titles and abstracts to identify potentially eligible articles. We will then obtain the full text of each potentially eligible study and assess in details prior to inclusion. Two assessors will independently extract data from full text articles using a standardised data collection form. The methodological quality of each study is assessed using the Quality Assessment of Diagnostic Accuracy Studies version 2 (QUADAS -2) tool.[1] Heterogeneity will be assessed using the bivariate model with covariates. We will contact the authors of relevant papers to determine whether they are aware of unpublished data.

References

1. Macaskill P, Gatsonis C, Deeks JJ, Harbord R, Yemisi Takwoingi Y. Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy. Chapter 10: Analysing and presenting results.

4.2. Comparison of the two CT techniques

Trial design has already been through the Trust R&D process and received approval and statistical advice for trial numbers have been estimated. Scanner time and funding has been identified. Medical physics have completed dose estimations. The ethics process has begun. The funding for the students salary is from a combination of the PenCLAHRC funding offered and funding secured through the Director of R&D at Derriford Hospital (Professor Simon Rule).

This study is very similar in terms of recruitment and data analysis to a number of recent MD & PhD students. We therefore see no major obstacles.

Protocol

a. Trial Participants

Overall Description of Trial Participants

Patients with cancer undergoing a routine CT chest abdomen and pelvis (CT TAP)

Inclusion Criteria

- Patients having routine follow up cancer CT TAP scan
- Age more than or equal to 40 years of age at the time of scan.
- Able to provide informed written consent
- Able to follow verbal commands for breath holding and remain still for the duration of scanning

Exclusion Criteria

- Patient unable to give informed consent.
- Patients unable to lie supine
- Patient not able to breath hold for at least 10 seconds.
- Patients not having regular heart rate. Patient with atrial fibrillation or >2 atrial or ventricular premature beats on a preoperative 12 lead ECG (suboptimal image quality results from irregular heart rhythms)
- Patient having eGFR <30, to avoid risk of contrast nephrotoxicity in patients potentially at risk) or chronic renal failure on dialysis
- Patient has known contrast reaction.
- Patient is pregnant.
- Patients BMI>35
- Unavailability of research slot to accommodate for the urgency of the scan requested.

Number of patients planned for observational study:
80
This is on the basis of 0.95 proportion of agreement between the two tests and lower limit of non-inferiority between the tests being 0.9.

b. Feasibility
Approximately 30 patients per week are scheduled for outpatient CT for cancer follow-up for monitoring or recurrence. These scans are often deemed routine but are prospectively planned in advance (usually appointment booked from a few weeks to months in advance). Eligible patients will be identified in advance. We have approached patients scheduled for outpatient CT scanning and asked them if they would be willing to participate in the study on a hypothetical basis. Out of 25, 14 said they would be willing to participate. We also have data from a previous CT Research project, which puts recruitment at around 56%. In the current study if we recruit 4-6 patients per week (as there are limited slots in research scan time) we estimate the study to take around 6 months. Under guidance of a radiation Physicist we have successfully performed preliminary feasibility trial in a phantom model.

Summary of Trial Design

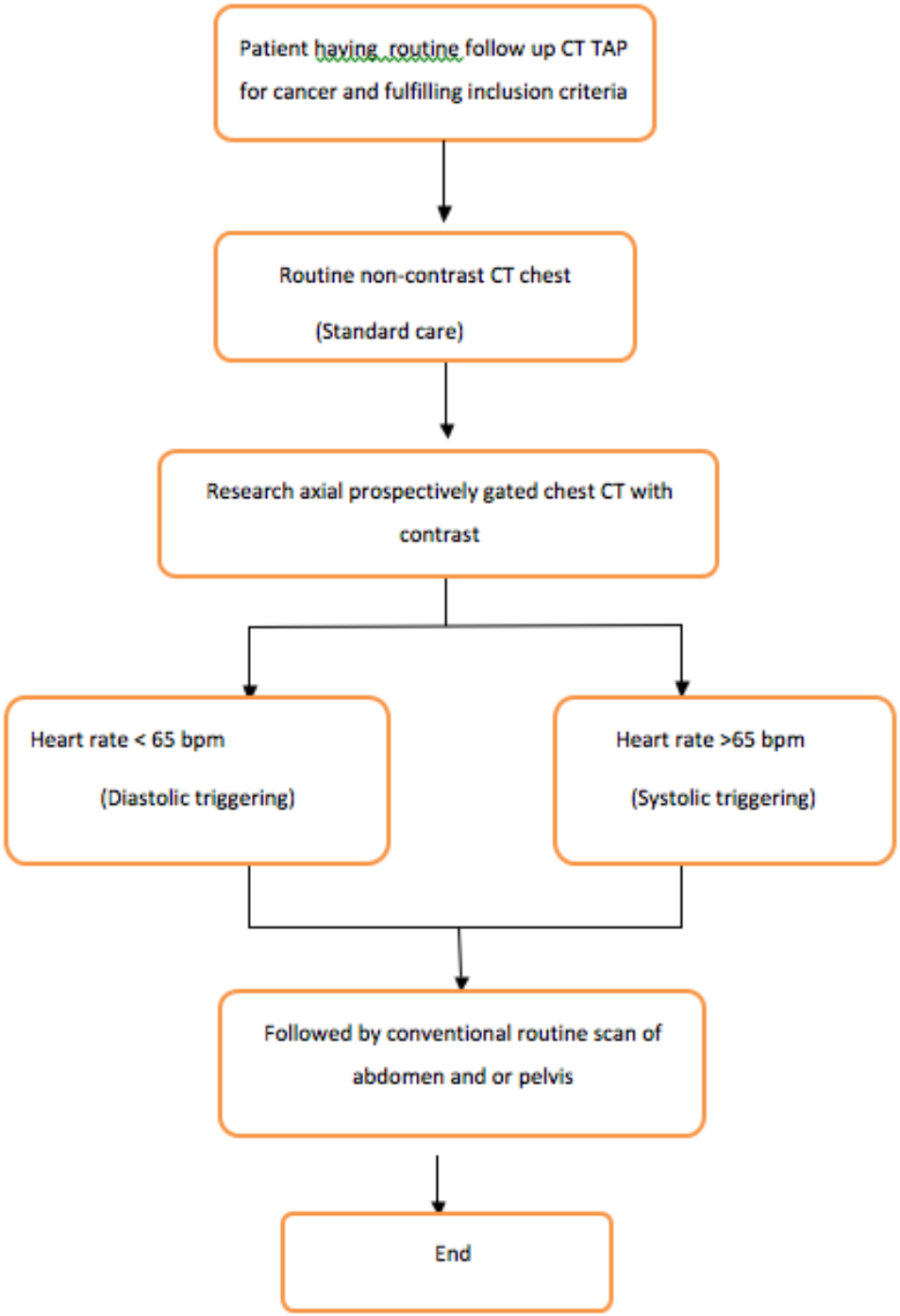


IMAGE ANALYSIS

Once recruitment has begun scans will have to be anonymised and interpreted. The student will be involved in the later using the below techniques. This will take @ 6 months.

Image quality between the two types of scan will be performed both objectively and subjectively using established technique below. Of note the team have had extensive experience of such methodology when analyzing the applicability of low dose CT (the subject of V. Vardhanabhuti's PhD) and have published widely on the techniques.

Primary Objective; Image quality will be measured

- *Objectively*:
  1) Calculating image noise as measured by standard deviation (SD) in a region of interest.
  2) Calculating contrast-to-noise ratio (CNR)
- *Subjectively*:

All image data sets will be presented in blinded and randomized manner to two experienced consultant radiologists. Subjective image quality will be assessed in terms of subjective image noise, subjective image contrast, lesion conspicuity, diagnostic confidence and artefacts. The image quality attributes are taken from the European Guidelines on Quality Criteria for Computerized Tomography document and have been proven to be robust in comparing subjective image quality.

Secondary Objective: Dose estimation and coronary segment analysis

Dose estimation: The total exam dose-length product (DLP) displayed by the CT scanner at the end of each CTPA is recorded[15]. The effective dose in mSv is calculated by multiplying the total DLP for each exam by the conversion coefficient for the chest of 0.014 (as taken from National Radiological Protection Board Document[16]).

Coronary segments analysis: Image quality of the 4 main coronary arteries (left main, left anterior descending, left circumflex, and right coronary artery) was determined based on a 4-point grading system[14] as follows:

Score:

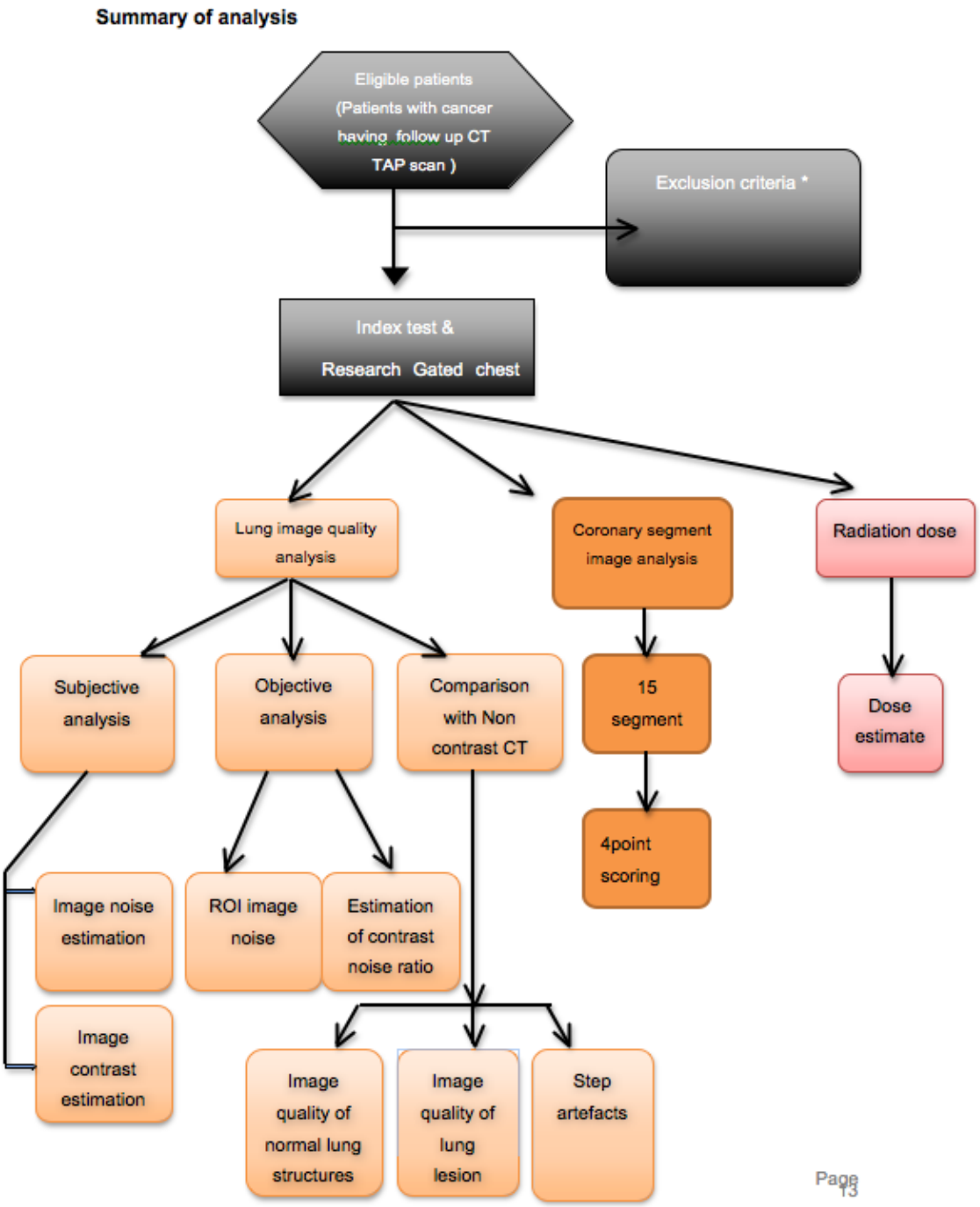
1 – **Non-diagnostic**: impaired image quality that precluded appropriate evaluation of the coronary arteries due to severe motion artefacts, extensive coronary calcifications, severe image noise, or insufficient contrast;

2 - **Adequate**: reduced image quality because of artefacts due to motion, image noise, or low contrast attenuation, but sufficient to rule out significant stenosis;

3 - **Good**: presence of artefacts caused by motion, image noise, coronary calcifications, or low contrast, but fully preserved ability to assess the presence of luminal stenosis as well as the presence of calcified and non-calcified coronary atherosclerotic plaque;

4 - **Excellent**: complete absence of motion artefacts, strong attenuation of vessel lumen, and clear delineation of vessel walls, with the ability to assess luminal stenosis as well as plaque characteristics.

Following analysis a further 6 months will be required for analysis and writing up.



3. **Quantifying the additional predictive ability**

Assuming that the feasibility of prospective gated CT is demonstrated, the next step will be to quantify the potential improvement of the ability to predict cardiac risk. The best existing prediction algorithm will be identified from the systematic review in 1. and compared with information provided by the prospective gated CT (either alone or in combination with existing risk predictors. We envisage this will require further primary data collection of considerable scale, so it may be that only a pilot study for a full study is achievable within the PhD.

A full proposal for this final piece of work will be developed by the candidate with advice from the supervisors before proceeding.

If prospective gated CT scanning for any reason emerges as being unfeasible, there will be many alternative options for a third piece of work to complete the PhD, pursuing the general problem of improving identification of cardiac risk using new imaging techniques ahead of major operations

4. Relevance/significance.

Should our initial study prove that it is indeed possible to perform prospectively gated CT (with no detriment to analysis of other structures or increase in radiation dose) this will open up the potential for a number of studies on the identification of “silent” coronary artery disease. Should its identification prove clinically useful it is possible that the technique will become the standard method of assessment for all patients undergoing CT of the chest. As such it could change Radiology practice world-wide with considerable potential patient benefit.

References

1. Coronary heart disease statistics A compendium of health statistics 2012 edition. Nick Townsend, Kremlin Wickramasinghe, British Heart Foundation Health Promotion Research Group. Department of Public Health, University of Oxford

2. Myocardial injury after noncardiac surgery: a large, international, prospective cohort study establishing diagnostic criteria, characteristics, predictors, and 30-day outcomes. Anesthesiology. 2014 Mar;120(3):564-78

3. Systematic review of the clinical effectiveness and cost-effectiveness of 64-slice or higher computed tomography angiography as an alternative to invasive coronary angiography in the investigation of coronary artery disease. HTA review 2008:12no 17

4. Risk stratification using CT coronary angiography in patients undergoing intermediate-risk surgery. JACC 2013;61:661