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Document: Protocol

Official Study Title: Comparison of Myocardial Blood Flow Measurements with Dedicated Solid State SPECT Camera Imaging versus PET Imaging

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Comparison of Myocardial Blood Flow Measurements with Dedicated Solid State SPECT Camera Imaging versus PET Imaging

Principal Investigator: Terrence D. Ruddy, MD, FRCPC

Co-Investigators: Benjamin Chow, MD, FRCPC
Rob deKemp, PhD
Ran Klein, PhD
Glenn Wells, PhD

Study Centre
The University of Ottawa Heart Institute at the Ottawa Hospital

Study Funding Support
GE Healthcare,
Global Research Headquarters
9900 Innovation Drive,
Wauwatosa, Wisconsin, United States, 53226

Protocol Version 4: August 2, 2018

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Clinical Protocol Synopsis

Study Title: Comparison of Myocardial Blood Flow Measurements with Dedicated Solid State SPECT Camera Imaging versus PET Imaging

Version 4: August 2, 2018

Study Centre

University of Ottawa Heart Institute

Study Objectives

1. To evaluate the correlation of global and regional myocardial blood flow (MBF) measurements and calculated myocardial flow reserve (MFR) using single photon emission computed tomography (SPECT) and ^{99m}Tc-tetrofosmin (^{99m}Tc) to positron emission tomography (PET) with Rubidium-82 (Rb-82) or N-13-ammonia ($^{13}NH_3$) in patients with an intermediate to high probability of CAD (Phase 1);

2. To determine the reproducibility of global and regional myocardial blood flow measurements and calculated myocardial flow reserve using SPECT and ^{99m}Tc-tetrofosmin in patients with an intermediate to high probability of CAD (Phase 2);

3. To evaluate the correlation of global and regional myocardial blood flow measurements and calculated myocardial flow reserve using SPECT and ^{99m}Tc-tetrofosmin to PET with Rb-82 or $^{13}NH_3$ in normal volunteers (Phase 3).

Hypotheses

1. The correlation of global and regional myocardial blood flow measurements and calculated myocardial flow reserve using SPECT to PET in patients with an intermediate to high probability of CAD will be $r > 0.6$ (Phase 1);

2. The test-retest reproducibility of global and regional myocardial blood flow measurements and calculated myocardial flow reserve using SPECT in patients with an intermediate to high probability of CAD will be within10 to 15% (Phase 2);

3. The correlation of global and regional myocardial blood flow measurements and calculated myocardial flow reserve using SPECT to PET in normal volunteers will be $r > 0.6$ (Phase 3).

Study Type

Investigator-initiated, imaging research.

Study Design

For the Phase 1 correlation study, participants will undergo a standard clinical rest/stress PET study with either Rb-82 or $^{13}NH_3$ with a low dose CT and a rest/stress SPECT study with ^{99m}Tc within a 4 week period. Participants with CAD will be recruited from patients already referred for clinical SPECT or PET imaging and with an intermediate to high probability of CAD. Any participants who have an intervention or undergo a significant cardiac event during the 4 week interval will be excluded.

For the Phase 2 reproducibility study, participants will be recruited from patients already referred for clinical rest/stress SPECT imaging and with an intermediate to high probability of CAD. Participants will undergo a second rest/stress SPECT with ^{99m}Tc within a 4 week period. Any participants who have an intervention or undergo a significant cardiac event during the 4 week interval will be excluded.

For the Phase 3 correlation study, normal volunteer participants will undergo a standard rest/stress PET study with either Rb-82 or $^{13}NH_3$ with a low dose CT and a rest/stress SPECT study with ^{99m}Tc within a 4 week period.

Number of Participants

For the correlation studies (hypothesis 1 and 3), two specific populations including 1) 30 participants with an intermediate to high probability of CAD (Phase 1) and 2) 30 healthy volunteers without known heart disease (Phase 3).
For the reproducibility study (hypothesis 2), 30 participants with an intermediate to high probability of CAD (Phase 2).

Inclusion and Exclusion Criteria

Inclusion Criteria

For all participants

- Age ≥ 18 years old
- BMI ≤ 40 kg/m^2
- Able and willing to comply with the study procedures

1. Participants with an intermediate to high probability of CAD
   - Suspected or known CAD on a stable medication regime

2. Healthy volunteers without known heart disease OR
   - Low risk of CAD (ACC Guidelines Pre-test Probability of CAD by Symptoms, Gender and Age)

Exclusion Criteria:

- History or risk of severe bradycardia (heart rate < 50 beats per minute) not related to chronotropic drugs

- Known second- or third-degree AV block without pacemaker
- Dyspnea (NYHA III/IV), wheezing asthma or severe COPD
- Coronary artery bypass graft (CABG) surgery within 60 days prior to screening or at any time after consent
- Percutaneous coronary intervention (PCI) within 30 days prior to screening or at any time following consent
- Acute myocardial infarction or acute coronary syndrome within 60 days prior to screening or at any time following consent
- Recent use of dipyridamole-containing medications (e.g. Aggrenox)
- Known hypersensitivity to dipyridamole
- Breastfeeding or pregnancy
- Claustrophobia or inability to lie still in a supine position
- Unwillingness or inability to provide informed consent

Study Duration for Participants

Duration of participation is a maximum of 4 weeks. No changes to clinical care in the CAD population will be made.

Safety and Tolerability

Safety variables will include the recurrence of procedure related adverse events. Adverse events (AE) and serious adverse events (SAE) will be defined and reported according to regulatory standards. AEs and SAEs will be reported from the signing of the consent and followed until resolution or determined to be not clinically significant.

Statistical Methods

For the correlation studies, global and regional MBF measurements acquired using SPECT and PET and calculated MFR measurements will be correlated with Spearman correlation analysis. For the reproducibility study, Bland-Altman plots will be used to determine significant bias and the coefficient of repeatability of global and regional MBF measurements acquired using SPECT and calculated MFR.

Abbreviations

3D	three dimensional
ACC	American College of Cardiology
AC	attenuation correction
AE	Adverse Event
AV	atrial-ventricular
BMI	body mass index
CABG	coronary artery bypass graft
CAD	coronary artery disease
CRF	case report form
COPD	chronic obstructive pulmonary disease
CT	computed tomography
g	gram
ICH GCP	International Conference on Harmonization Good Clinical Practice
kg	kilograms
kVp	kilo-volt potential
MBF	myocardial blood flow
MBq	megabequerels
mcg	micrograms
mCi	millicurie
MFR	myocardial flow reserve
mg	milligrams
min	minute
mm	month
MRN	medical record number
mSv	milliseverts
$^{13}NH_3$	Nitrogen-13-ammonia
NC	no correction
NYHA	New York Heart Association
OHSN-REB	Ottawa Health Science Network Research Ethics Board
PET	positron emission tomography
PCI	percutaneous coronary intervention
PHI	Personal Health Information
^{82}Rb	Rubidium-82 Chloride
SAE	Serious Adverse Event
SC	scatter correction
SPECT	single photon emission computed tomography
SOP	Standard Operating Procedures
^{99m}Tc	Technetium-99m
^{201}Tl	Thallium Chloride
TOH	The Ottawa Hospital
UOHI	University of Ottawa Heart Institute
yyyy	year

1. Introduction

1.1 Background and Rationale

Absolute myocardial blood flow (MBF) and myocardial flow reserve (MFR) using positron emission tomography (PET) provide additional diagnostic and prognostic power compared to relative perfusion results [1-7]. Myocardial perfusion imaging is much more widely carried out with single photon emission tomography (SPECT) than with PET. However, measurements of MBF or MFR are rarely obtained with SPECT due to technical reasons (need for attenuation and scatter correction and the requirement of the camera to rotate around the patient for 3-dimensional imaging). An estimate of MFR without a direct measurement of MBF can be determined with a combination of dynamic planar followed by static SPECT acquisitions [8] and provides useful prognostic information [9]. Dynamic tomographic data can be acquired with rapid rotation of SPECT camera and provide 1) a measure of MFR [10] and 2) the arterial input function [11] suggesting that accurate measures of MBF could be possible with SPECT [12].

The recent development of dedicated solid state cardiac SPECT cameras has made the possibility of MBF measurement much more feasible and practical. Cameras such as the NM 530c/570c cameras (GE Healthcare, Haifa, Israel) and the DSPECT system (Spectrum Dynamics Medical Inc., Palo Alto, CA) have greatly improved sensitivity and are stationary [13]. These features allow dynamic imaging with high temporal resolution and improved count density and facilitate MBF measurement with SPECT. Recent work has shown the capability to provide an index of global MFR [14], but no studies have demonstrated measurement of MBF.

For the first time, Dr. Glenn Wells and our group recently demonstrated the accurate quantification of MBF in a pig model of rest and transient occlusion at stress [15]. Data were acquired using attenuation and scatter corrected dynamic SPECT data with a NM 530c camera with ^{201}Tl, ^{99m}Tc-tetrofosmin and ^{99m}Tc-sestamibi. MBF was measured with gold-standard microspheres injected simultaneously with the SPECT tracers. Measured extraction fraction data agreed with those obtained previously using invasive techniques. MBF determined using the measured extraction fractions produced accurate values and good correlations with microsphere MBF between $r=0.75$ and $r=0.83$ ($p<0.01$ for all) and the resulting correlation in the MFR was up to 0.89 ($p<0.01$). Thus, non-invasive measurement of absolute MBF with a stationary dedicated cardiac SPECT is feasible using common perfusion tracers.

The goal of this study is to compare SPECT and PET measurement of MBF and MFR and determine the reproducibility of SPECT MFR measurements in patients.

1.2 Hypothesis

1. The correlation of global and regional myocardial blood flow (MBF) measurements and calculated myocardial flow reserve (MFR) using SPECT to PET in participants with an intermediate to high probability of CAD will be $r > 0.6$ (Phase 1);

2. The test-retest reproducibility of global and regional MBF measurements and calculated MFR using SPECT in participants with an intermediate to high probability of CAD will be within 10 to 15% (Phase 2);

3. The correlation of global and regional MBF measurements and calculated MFR using SPECT to PET in normal volunteers will be $r > 0.6$ (Phase 3).

2. Study Objectives

1. To evaluate the correlation of global and regional MBF and MFR measured using SPECT to that measured using PET in participants with an intermediate to high probability of CAD (Phase 1);

2. To determine the reproducibility of global and regional MBF measurements and calculated MFR using SPECT in participants with an intermediate to high probability of CAD (Phase 2);

3. To evaluate the correlation of global and regional MBF and MFR measured using SPECT to that measured using PET in normal volunteers (Phase 3).

3. Study Design

<u>Phase 1:</u>
Patients referred to the University of Ottawa Heart Institute Diagnostic Imaging Department for myocardial perfusion imaging (MPI), PET or SPECT, will undergo a clinically indicated rest/stress PET scan using either Rb-82 or $^{13}NH_3$. Research imaging will consist of a rest/stress SPECT scan with ^{99m}Tc completed with 4 weeks of the PET scan, occurring either before or after the PET scan.

Study end will be defined as the completion of both the PET and SPECT scans.

<u>Phase 2:</u>
Patients will undergo a clinically indicated rest/stress SPECT scan as referred. Research imaging will consist of a second rest/stress SPECT scan with ^{99m}Tc within 4 weeks of the clinical SPECT scan.

Study end will be defined as the completion of both SPECT scans.

Phase3:
Normal volunteers will undergo a rest/stress PET scan using either Rb-82 or $^{13}NH_3$ and a rest/stress SPECT scan with ^{99m}Tc completed within a 4 week period.

Study end will be defined as the completion of both the PET and SPECT scans.

4. SPECT and PET Imaging

4.1 ^{99m}Tc SPECT Imaging

The camera used in this study will be the Discovery NM 530c (GE Healthcare, Haifa, Israel). This camera is a dedicated cardiac camera that uses 19 cadmium-zinc-telluride (CZT) based detectors [16]. Each detector is 8 x 8 cm divided into a 32x32 array with a pixel pitch of 2.46mm. Each detector has a single-pinhole collimator with an effective diameter of 5.1mm. The detectors are arranged in an arc around the field-of-view, providing sufficient angular sampling for 3D reconstruction without the need to rotate the camera. The sensitivity of the system is approximately 4-times higher than a standard dual-head gamma camera.

Participants will be instructed to fast for a minimum of 4 hours and to abstain from products containing caffeine for 24 hours prior to imaging.

^{99m}Tc-tetrofosmin (370 MBq (2.8 mSv) for rest and 1100 MBq (7.7 mSv) for stress) will be delivered using a power injector as a 9 ml bolus over 30 s followed by a 9 ml saline flush over 30 s. Image data will be acquired in listmode for 11 min starting just prior to tracer injection. Resting images will be acquired first and repeated just prior to stress. For stress, dipyridamole (0.14 mg/kg/min over 5 min) will be given intravenously. At 8 minutes following onset of dipyridamole infusion, stress imaging will start prior to the ^{99m}Tc-tetrofosmin injection. Aminophylline will be administered intravenously at 11 minutes following onset of dipyridamole infusion. The usual post-stress images will be acquired approximately 45 minutes after radiotracer injection.

Following acquisition, the listmode data will be rebinned into 9x10s, 6x15s, 4x120s frames. The projection data for each frame will be independently reconstructed using manufacturer supplied MLEM iterative reconstruction that includes point-spread function modeling and a noise-suppression prior. A total of 30 iterations will be used corresponding to the manufacturer recommendation for resting (low-count) studies. Images will be filtered post-reconstruction using a 3D 5^{th}-order Butterworth filter with a cut-off frequency of 0.37 cycles/cm. Images will be reconstructed without corrections (NC), and with attenuation correction (AC) and scatter correction (SC). When applied, AC will be based on the CT scan from the PET/CT acquisition which will be coregistered manually to the emission reconstruction using on-line quality assurance tools. SC will be applied to the projection data prior to reconstruction using a dual-energy window approach [15]. For the Phase 2 SPECT reproducibility study, an additional CT scan will be acquired on an Infinia/Hawkeye 4 SPECT/CT gamma camera and used in place of the CT from the PET/CT acquisition.

The reconstructed dynamic image series will be processed using FlowQuant (Ottawa, ON), our in-house kinetic analysis software [17] as well as Infinia (GE Canada). With this semi-automatic software, a 1-tissue-compartment model will be fit to the myocardium time-activity data to generate a parameterized map of the uptake rate constant K1 (ml/min/g) for the heart. K1 values will be scaled to MBF based on the K1-MBF relationship determined from the pig studies (15). Finally, the results from the FlowQuant (Ottawa, ON) will be compared to those of the commercially released Infinia software (GE Canada) to determine the similarities between the two software packages.

4.2 ^{82}Rb / $^{13}NH_3$ PET Imaging

Rb-82 or $^{13}NH_3$ PET Imaging will be performed according to the UOHI standard clinical protocol [18]. Briefly, the participants will be positioned in a 3D PET system (GE Discovery 690 PET/VCT). The initial rest PET scan will include a low-dose CT for attenuation correction (0.4 mSv; fast helical 2 s, 120 kVp with axial and angular mA-modulation at noise-index = 50). Hyperemic stress flow will be induced with dipyridamole (0.14 mg/kg/minute for 5 minutes). PET imaging will be performed using 1000 MBq (0.73 mSv) of Rb-82 or 3 MBq/kg (0.7 mSv) of $^{13}NH_3$ at rest and during stress with radiotracer injected 8 minutes following the start of dipyridamole infusion. MBF and MFR will be quantified and polar-maps generated for each rest and stress state using in-house FlowQuant© software [17] as well as Infinia (GE Canada).

4.3 Concentration of ^{99m}Tc SPECT tracer

SPECT perfusion tracers are known to bind to red blood cells limiting the amount of tracer available to the myocardium for extraction [15]. Thus, concentration function used in the kinetic analysis is better represented by the plasma concentration of tracer instead of the whole blood concentration, as measured by the image-based methods used in this study. Correction for the plasma to whole blood ratio can be done by applied using a correction curve. The correction curve has been determined with pig experiments but needs to be calibrated to humans. To estimate this correction, we will measure the whole-blood to plasma tracer concentration ratio at equilibrium (~30min post injection) which will then be used to rescale the full curve that was measured in the pig study. For this purpose, a 12ml blood sample (2x6ml) at 30min after the rest tracer injection and a 2nd 12ml (2x6ml) blood sample at 30min will be drawn after the stress injection. Whole blood and serum aliquots will be prepared and then measured in a well-counter to determine the concentration ratio.

5. Sample Size and Statistical Analysis

The sample size for the correlation studies (hypotheses 1and 3) was calculated to provide a 95% confidence interval around r=0.6 that excludes r=0.25, which is considered the upper bound of no correlation. To obtain a difference in the z-transform of r=0.6 and r=0.25 of 1.96 requires an n of 24. A withdrawal rate of 10 to 15 % increases the number of patients required to 30 per group.

The sample size for the reproducibility study (hypothesis 2) is estimated to detect a 10% difference on background of 15% variability (assuming a SPECT MBF uncertainty similar to the high end of PET variability). This requires a sample size of 26 (power = 0.95; alpha =0.05). A withdrawal rate of 10 to 15 % increases the number of patients required to ~ 30 per group.

Adverse events will be listed on an individual basis. All safety variables and demographic data will be tabulated with descriptive statistics, if appropriate.

For the correlation studies global and regional MBF measurements acquired using SPECT and PET and calculated MFR will be correlated with Spearman correlation analysis. For the reproducibility study Bland-Altman plots will be used to determine significant bias and the coefficient of repeatability of global and regional MBF measurements acquired using SPECT and calculated MFR.

6. Study Population

6.1 Source of Participants

The CAD study population will be adult male and female patients who are referred to the outpatient cardiology clinics and/or the non-invasive Diagnostic Imaging Department at the University of Ottawa Heart Institute (UOHI). The healthy volunteer population will be recruited from the Diagnostic Imaging Department or by the use of advertisements/posters located in UOHI and/or The Ottawa Hospital (TOH).

6.2 Inclusion Criteria

<u>For all participants</u>

- Age ≥ 18 years old
- BMI ≤ 40 kg/m^2
- Able and willing to comply with the study procedures

<u>Participants with intermediate to high probability of CAD</u>

- Suspected or known CAD on a stable medication regime.

<u>Healthy volunteers without known heart disease</u>

- Low risk of CAD (ACC Guidelines Pre-test Probability of Coronary Disease by Symptoms, Gender and Age)

6.3 Exclusion Criteria

- History or risk of severe bradycardia (heart rate < 50 beats per minute) not related to chronotropic drugs
- Known second- or third-degree AV block without pacemaker
- Dyspnea (NYHA III/IV), wheezing asthma or severe COPD
- Coronary artery bypass graft (CABG) surgery within 60 days prior to screening or at any time after consent
- Percutaneous coronary intervention (PCI) within 30 days prior to screening or at any time following consent

- Acute myocardial infarction or acute coronary syndrome within 60 days prior to screening or at any time following consent
- Recent use of dipyridamole-containing medications (e.g. Aggrenox)
- Known hypersensitivity to dipyridamole
- Breastfeeding or pregnancy
- Claustrophobia or inability to lie still in a supine position
- Unwillingness or inability to provide informed consent

6.4 Withdrawal from Study

Participants may withdraw from the study at any time without penalty or prejudice. No data will be collected from the time of withdrawal.

6.5 Early Termination

Participants may be terminated for reasons such as, but not limited to:

- Noncompliance with study procedures.
- Participant experiences a cardiac event.
- Secondary illness requiring intervention during the study.
- Pregnancy.
- Participant safety may be compromised in the opinion of the investigator.
- Study may be stopped at the request of a regulatory authority or the REB.

If study discontinuance occurs, the date and reason must be documented in the CRF. If the participant is lost to follow-up, documentation must be made as to the steps taken to contact the participant. Every attempt will be made to perform end of study follow-up with the participant who withdraws or is terminated.

7. Data Collection

All participant information and data will be collected respecting participant confidentiality and privacy and following written informed consent.

7.1 Demographic Information

Demographic information will include the participant's date of birth (mm/yyyy), gender, height and weight.

7.2 Medical History

Medical history and results from any standard of care testing related to a participant's cardiovascular disease and inclusion/exclusion criteria will be collected. Clinical data obtained at scan visits will be included as part of the study data.

7.3 Clinical Status

The blood pressure, heart rate and clinical status will be monitored according to current clinical protocols during imaging procedures. Clinical protocol will be followed for dipyridamole stress testing.

7.4 Caffeine Ingestion

The ingestion of caffeine will be restricted for 24 hours prior to all imaging procedures as per standard clinical practice.

7.5 Pregnancy Assessment

A woman of child bearing potential will have a urine pregnancy test performed on the days of imaging.

8. Risk Benefit Assessment

8.1 SPECT and PET Imaging

Phase 1:
Participants undergoing SPECT/CT imaging with ^{99m}Tc will receive a total radiation dose of 10.5 mSv (rest dose 2.8 mSv and stress dose 7.7 mSv)

Phase 2:
Participants undergoing research SPECT/CT imaging with ^{99m}Tc will receive a total radiation dose of 10.9 mSv (rest dose 2.8 mSv and stress dose 7.7 mSv) and one SPECT CT attenuation scan (0.4 mSv)).

Phase 3:
Participants undergoing PET imaging with Rb-82 and SPECT imaging with ^{99m}Tc will receive a total radiation dose of 12.6 mSv (10.5 mSv for the SPECT and 2.1 mSv for the PET, including low-dose CT (0.4mSv) attenuation scan).

Participants undergoing PET imaging with $^{13}NH_3$ and SPECT imaging with ^{99m}Tc will receive a total radiation dose of 12.3 mSv (10.5 mSv for the SPECT and 1.8 mSv for the PET, including low-dose CT (0.4mSv) attenuation scan).

8.2 Dipyridamole Pharmacological Stress

Dipyridamole is a vasodilator commonly used in the clinical practice of nuclear cardiology and will be used as the stress agent for all stress studies. Rare serious adverse reactions associated with the administration of intravenous dipyridamole for MPI have been reported. These have included fatal and non-fatal myocardial infarction, ventricular fibrillation, symptomatic ventricular tachycardia, stroke and transient cerebral ischemia. The infusion rate is monitored to minimize this risk and the symptoms can generally be reversed with an intravenous injection of 50 - 250 mg of aminophylline over several minutes.

9. Safety and Tolerability

9.1 Safety Variables

Safety variables will include the occurrence of procedure-related adverse events and changes in clinical status.

9.2. Safety Reporting

Adverse events (AE) and Serious Adverse Events (SAE) will be defined and reported according to ICH/GCP and Regulatory Standards. AEs and SAEs will be reported from the signing of the consent and followed until resolution or determined to be not clinically significant.

9.3 Pregnancy

During the conduct of the trial should a pregnancy be actual (positive result with testing) or suspected, the participant will be advised to contact the Investigator immediately. Participation in the trial will be terminated.

10. Study Records

Study files will be divided into two categories: Investigator Study Files and Participant Clinical Trial Files. Study files will be retained for a period of 25 years from the study end. GE Healthcare will have access to de-identified data and images plus other deliverables which are generated from this study as specified in the contractual agreement.

10.1 Investigator Study Files

Regulatory files will contain all essential documents relating to trial conduct and management including Ottawa Health Science Network Research Ethics Board (OHSN-REB) and regulatory communications.

10.2 Participant Clinical Trial Files

The participant files will include the consent form, screening and enrollment logs, Master List, source documents and the case report form (CRF). Personal Health Information (PHI) relevant to the conduct of the trial will be collected and will include medical history, inclusion and exclusion criteria details, medical records generated during the conduct of the trial and medical record number (MRN). These documents will be maintained as paper and electronic files under the responsibility of the Principal Investigator.

11. Monitoring/Access to Files for Inspection

The investigator agrees to provide access to all study related files for conduct of inspections or auditing by regulatory authorities.

Ongoing review of safety parameters and events will be recorded and reported according to applicable regulations and OHSN-REB requirements. No formal Data Safety Monitoring Board will be specified due to the low level of risk associated with this trial.

Periodic study monitoring will be conducted to assure adherence to the protocol, ICH GCP guidelines and that data is accurate, complete and verifiable. An internal monitoring plan, following local SOPs, will be developed. The designated internal monitor will have the training and qualifications necessary to provide an appropriate and thorough

verification of the study files. Confidentiality will be consistent with local requirements and national regulations.

12. Publication

Review and Publication will be according to contractual agreements in place at the time of the trial.

13. Budget

This investigator initiated study will be funded by a research grant from GE Healthcare with funding for 2 years to carry out the Phase 1 (Correlation in CAD participants) and Phase 2 (Reproducibility studies). Funding for a third year for the Phase 3 study will be negotiated during year 2. The necessary software licences for acquisition and processing of image data will be provided by GE Healthcare for the 2 year duration of the project.

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