MODULE ONE:
CORE APPLICATION FORM AND CHECKLIST

State Government Victoria Department of Human Services

BEFORE YOU BEGIN

This Application Form is for use by researchers proposing to conduct a research project involving humans. **All researchers must complete Module 1** and may have to complete other Modules (see checklist at Question 1.6).

Before you start this application, please read the **Module One: Core Application Guidelines** and the National Health & Medical Research Council's *National Statement on Ethical Conduct in Research Involving Humans* (1999).

Please do not delete the version date in the footer e.g. July 2006.

Office Use Only:

HREC Ref. No._____	**Date of Approval: / /**
Approval Period: / /	**From / / To**

SECTION A: PROJECT OVERVIEW

1.1 Application Date: 12th January 2010

1.2 Full Project Title

Physiology of Acute Coronary syndromes: Focus on inflammation and microvascular dysfunction.
FOR CLINICAL TRIALS ONLY: **Company/Sponsor Protocol Number (if applicable):** **Version:** **Date:**

1.3 Brief Lay Summary of the Project

Briefly describe the project. Refer to the Guidelines for the type of information and level of detail required in your response *(no more than one page)*

Myocardial infarction ('Heart attack') remains a significant cause of morbidity and mortality. Despite re-opening blocked or narrowed heart arteries, there is still a group of patients that have a worse outcome due to disease of smaller arteries, not visible with conventional diagnostic x-ray imaging. A tool that directly measures involvement of the smaller arteries at the time of coronary intervention would therefore be desirable. The index of microvascular resistance is such a technique that uses a special pressure wire to look at changes in flow in heart arteries in order to calculate resistance within the smaller vessels. We plan to use this tool in patients undergoing percutaneous coronary intervention (PCI) who present with chest pain or with heart attacks to assess the small vessel (microcirculatory) involvement. We will also investigate the role of microvascular inflammation in the development of peri-procedural PCI myocardial infarction (MI). We will perform tests to identify factors that could lead to small artery disease either locally, by looking at the 'cholesterol' (atherosclerosis) deposits on the vessel wall using a special imaging technique. And as part of a systemic process such as inflammation, by looking at blood markers that correlate with inflammation, blood cell function and calculating IMR pre and post PCI. To do this research we will require approximately 40 patients who have had a suspected heart attack or angina who are scheduled to undergo an invasive assessment of the blood supply to their heart and require PCI. During this assessment we will measure flow within the heart blood vessels using a special flow wire and look at the blood vessel wall itself for cholesterol deposits (plaque) with a novel catheter-based infrared light camera. We will also take a small amount of blood to look at specific blood tests that show degrees of inflammation and the function of blood cells. We will assess the effect of colchicine (a mediction with known anit-inflammatory properties) on small blood vessel function. The goals of this study are to investigate the role of microvascular inflammation on the development of periprocedural PCI MI and assess factors that influence the function of the small blood vessels. We will utilise the above techniques in order to improve treatment for all patients who require PCI for a heart attack or angina and improve our understanding of the disease process and ultimately provide new treament options that may benefit the Australian community.

1.4 Relationship to Other Projects

Indicate whether the project is

☐ a new stand-alone project

X a sub-component of a previously approved project

☐ related to other previously approved projects (e.g. a follow-up study)

If the project is a sub-component of, or in some other way related to, a

previously approved project, provide project numbers for the other project(s). Also indicate which HREC(s) approved the other project(s).

HREC 010/10

1.5 Broad Category of Research

Tick the category which best fits the application:

☐ Social Science X Clinical Research

☐ Psychological ☐ Clinical Drug or Device Trial ⇨ CTN ☐ or CTX ☐

☐ Public Health ☐ Other (please specify) ……

1.6 Project Summary

Does the project involve

- Participants? Yes X No ☐
  If yes, please complete section D of Module 1
- Collection, use or disclosure of information? Yes X No ☐
  If yes, please complete section E of Module 1
- Drug or device trial? Yes ☐ No X
  If yes, please complete Module 2
- Use of human tissues? Yes X No ☐
  If yes, please complete Module 3
- Human genetic research? Yes ☐ No X
  If yes, please complete Module 3
- Use of radiation? Yes X No ☐
  No
  If yes, please complete Module 4

1.7 Multi-Site Projects

Is the project a multi-site project? That is, does the project involve recruitment of participants at more than one site and/or collection of information from more than one organisation?

Yes ☒ No ☐

Does the project have to be reviewed by other HRECs?

Yes ☐ No X

Name **all Australian HRECs** to which this project has been or will be submitted. For each HREC, list all Australian sites involved in this project that are covered by the application to that HREC. If the number of sites for a particular HREC is very large (or unknown), such that listing individual sites is not feasible, indicate the number of sites covered by that HREC (*e.g. 50 primary schools or 20 out of 60 child care centres, etc*). Indicate the status of the application to other HRECs.

HREC	**Site**	**Status of application** (*e.g. not yet applied/approved/ rejected/pending*)
St Vincent's Health Human Research Ethics Committee-A	St Vincent's Hospital	Amendment approval Pending
St Vincent's Health Human Research Ethics Committee-A	Frankston Hospital	Amendment approval Pending

SECTION B: RESEARCHERS AND CONTACT INFORMATION

1.8 List all researchers involved in this project

*Copy this table and repeat for each **Principal Researcher**.*

Title and Name	Dr Jamie Layland
Appointment	Cardiologist
Department	Cardiology, SVHM
Institution	SVHM, Peninsula Health
Mailing address	Cardiac Investigations Unit, St Vincent's Hospital
Describe what this researcher will do in the context of this project	Recruit patients, coordinate study, supervise collection of tissues
Include a brief summary of relevant experience for this project	Practising Cardiologist. Clinical use of techniques involved.
Phone	0404 209 028
Fax	9288 4422
Mobile/pager	0404 209 028
email	jamielayland@hotmail.com

Title and Name	A/P Andrew MacIsaac
Appointment	Director of Cardiology
Department	Cardiology, SVHM
Institution	Melbourne University, SVHM
Mailing address	Cardiac Investigations Unit, St Vincent's Hospital
Describe what this researcher will do in the context of this project	Coordinate study, supervise, perform invasive assessments.
Include a brief summary of relevant experience for this project	Extensive clinical research experience, practising cardiologist, previous supervision of MD/PhD students.
Phone	9288 2211
Fax	9288 4422
Mobile/pager	
email	Andrew.Macisaac@svhm.org.au

Title and Name	A/P Robert Whitbourn
Appointment	Deputy Director
Department	Cardiology, SVHM
Institution	Melbourne University, SVHM
Mailing address	CIU, 1st Floor IPS, St Vincent's Hospital, Fitzroy
Describe what this researcher will do in the context of this project	Coordinate study
Include a brief summary of relevant experience for this project	Extensive clinical research experience
Phone	92884423
Fax	92884422
Mobile/pager	
email	Robert.Whitbourn@svhm.org.au

*Copy this table and repeat for each **Associate Researcher**.*

Title and Name	Dr Andrew Wilson
Appointment	Senior Research Fellow, Cardiologist
Department	DOM, 4th floor clinical science building. Cardiology Department SVHM.
Institution	Melbourne University, SVHM
Mailing address	Dept of Medicine, SVHM
Describe what this researcher will do in the context of this project	Supervise, perform invasive studies.
Include a brief summary of relevant experience for this project	Extensive clinical research experience, PhD, Post Doctoral fellowship at Stanford, Similar project (HREC 80/00), Practising Cardiologist
Phone	92882574
Fax	92882581
Mobile/pager	
Email	Andrew.Wilson@svhm.org.au

Title and Name	Dr David Tong
Appointment	Research Fellow
Department	Cardiology, SVHM
Institution	Melbourne University, SVHM, Peninsula Health
Mailing address	Cardiac Investigations Unit, SVHM
Describe what this researcher will do in the context of this project	Recruit and consent patients.
Include a brief summary of relevant experience for this project	Previous clinical research experience.

Phone	0422 345 084
Fax	03 8845 7073
Mobile/Pager	0422 345 084
Email	davidcktong@yahoo.com

1.9 Training

Will any of the researchers require extra training to enable their participation in this project?

Yes No X

If *Yes*, list the researchers, describe the training that is required and who will provide this training.

Researcher	**Training required**	**Who will provide training?**

1.10 Person to whom the HREC may also direct correspondence:

Title and Name	Dr Jamie Layland
Appointment	Cardiologist
Department	Cardiology, SVHM
Institution	SVH, Peninsula Health
Mailing address	As above
Phone	
Fax	
Mobile/pager	
email	

SECTION C: PROJECT DETAILS

1.11 Anticipated duration of project: __12__ months

1.12 Anticipated commencement date at this site: 15 / 1 /2010

1.13 Anticipated completion date at this site: 31 / 08 /2018

1.14 Detailed Project Proposal

If the project is a clinical drug or device trial DO NOT complete question 1.14, but move directly to question 1.15. The detailed project proposal for clinical drug or device trials is completed in Module 2.

(a) Project Checklist

Major Proposal Components	Page and/or section number in the proposal	Not Applicable
Literature review		☐
Rationale for project		☐
Hypothesis/research questions		☐
Aims		☐
Methodology		☐
Inclusion/exclusion criteria		☐
Randomisation procedures		☐
Statistical or other analyses		☐

(b) Project Proposal

Every application must be accompanied by a detailed proposal. You may type (or "paste") your detailed proposal directly into the text box below and/or you may attach pre-printed document(s) immediately following this page. Attachments should include brochures/pamphlets, questionnaires or surveys and any other relevant documents. **Ensure that all attachments are page numbered throughout.**

You should consult the Guidelines about the type of information that should be included in the detailed proposal.

Introduction:
Despite improvements in medical therapy, ischaemic heart disease and specifically myocardial infarction remains a leading cause of death in developed countries. It is known that in patients with acute myocardial infarction (AMI) there is improved prognosis with restoration of the epicardial coronary circulation, and more specifically, long term prognosis is directly related to adequacy of myocardial perfusion. However, the re-establishment of Thrombolysis In Myocardial Infarction (TIMI) III epicardial flow whilst attractive, does not equate to myocardial perfusion as there is a vast network of pre-arterioles and arterioles that also make up the coronary circulation. These smaller components of the coronary circulation are termed the microcirculation and are not visible macroscopically with conventional angiography and as a result of this, the function of the microcirculation is not easy to directly assess. Despite restoration of epicardial flow in patients following an AMI or angina, abnormal myocardial perfusion frequently persists which relates to associated microvascular dysfunction (MCD). Such a clinical scenario has been allied to a worse prognosis when compared to patients with a less severely affected microcirculation. Therefore it is important on clinical and prognostic grounds to quantify microcirculatory dysfunction at the time of coronary angiography in patients presenting with an AMI or angina. Previous methods to qualify and quantify microvascular dysfunction invasively have yielded techniques that are poor surrogates which, although useful, are either subjective, suffering from significant inter/intra observer variability or are affected by systemic haemodynamics and myocardial contractility.

Recently, a novel and reproducible technique has emerged that can quantify microcirculatory function called the index of microcirculatory resistance (IMR). It is a simple, catheter laboratory based technique that utilises a pressure/thermistor tipped guide wire. This technique has been validated in small numbers of animal and human subjects and is more reproducible and less affected by haemodynamics than other invasive measures of microcirculatory function. IMR has been shown to predict recovery of LV function and viability following successful primary PCI in the ST elevation myocardial infarction (STEMI) population. It has not been validated in large numbers of patients nor has it been utilised in the non-ST elevation myocardial infarction (NSTEMI) cohort. Whilst it is conceivable that the abnormal IMR result could be solely as a direct result of distal embolisation from thrombus or reperfusion injury leading to MCD, there may be other factors that contribute to the abnormal IMR value. Also IMR has been shown to be higher pre-PCI in patients who develop peri-procedural PCI myocardial ischaemia (MI) (24). We will investigate such factors in order to understand what contributes to an abnormal IMR.

Rationale:
In recent years it has become apparent that atherosclerosis, rather than being a

bland proliferative process is a state of continued inflammation involving the immune system and many other complex pathways. At the core of the pathogenesis of atherosclerosis is endothelial dysfunction that in turn may contribute to MCD and an abnormal IMR. Microvascular disease in patients with and without acute coronary syndromes (ACS) that will include, NSTEMI, stable and unstable patients will be evaluated. Specifically, we will measure IMR in order to quantify microvascular dysfunction. Certain plaque characteristics are known to be associated with a greater predisposition to MCD. A recent study looking at patients who had sudden cardiac death secondary to coronary thrombosis demonstrated specific lesions with a higher propensity for MCD. Established invasive imaging techniques (Optical Coherence Tomography (OCT)) are able to qualify specific plaque types as well as to quantify total plaque volume which may help in the prediction of MCD and hence an abnormal IMR. We will therefore be performing OCT examinations on patients in order to characterize plaque and assess its impact on the microcirculation.

Extensive research has implicated platelets' with a fundamental role in the pathogenesis of acute coronary syndromes. Markers of activated platelets have been shown to be higher in unstable compared with stable patients with coronary artery disease. Activated platelets may contribute to microvascular dysfunction by microembolisation and release of vasoactive/inflammatory substances. Increased platelet activation has also been shown to predict periprocedural MI in ACS patients undergoing PCI. Platelet activation, by measurement of monocyte-platelet aggregates has also been shown to correlate with microvascular complications in diabetic patients. We therefore plan to assess platelet activation by measuring specific platelet markers, in order to establish the role of platelet activation in microcirculatory dysfunction and in peri-procedural PCI MI.

Inflammation is a known cause of endothelial dysfunction and has been implicated in the risk of sudden cardiac death in patients with coronary artery disease. We will look at systemic markers of inflammation to investigate if markers of systemic inflammation correlate with MCD and an abnormal IMR. These systemic markers of inflammation include serum levels of hsCRP, interleukin (IL)-1ß, IL-18 and downstream IL-6. These interleukins have increased intracardiac production in patients who have had an ACS (25) and treatment with low-dose colchicine reduces their production (25).

Recently, colchicine, which is long-known to have anti-inflammatory properties and is widely used in inflammatory conditions, has merged as a potential 'novel' therapy for cardiovascular disease. A recent trial has shown that low-dose colchicine of 500mcg daily reduced the primary cardiovascular events in patients with stable coronary artery disease and had negligible adverse effect profiles (23). Therefore, we would like to assess the impacts of colchicine on microvascular disease in patients presenting for PCI using the

above mentioned laboratory techniques.

Methods:
We will recruit patients who present with chest pain syndrome or stablised ACS (excluding STEMI) who are planned to have a PCI. This will be an open label randomised control trial of 40 patients: 20 in each arm. If selected, randomisation will be a 1:1 fashion. All patients will receive standard medical and PCI care/therapy. In addition the treatment arm will receive colchicine orally, 6 to 24hours prior to coronary angiogram. The dose of colchicine will be 1mg followed by 0.5mg 1 hour later. This regimen has been used before by Martinez et al (25) assessing the effect of colchicine on local cardiac production of inflammatory cytokines in patients with ACS and is based on the treatment of acute gout. ACS in this project is defined as myocardial infarction, non Q-wave myocardial infarction and unstable angina in accordance with the GRACE registry. Stabilised ACS refers to stable troponin and CK that has already peaked prior to angiogram. Patients will undergo history and clinical examination and have an electrocardiogram prior to angiography in accordance with standard practice. Patients will provide a urine sample for assessment of albumin:creatinine ratio since renal impairment is associated with endothelial dysfunction and perhaps MCD. Assessment of renal function as well as urine analysis is considered standard practice in the assessment of patients with suspected ACS. Patients will have an echocardiogram within 24 hours of angiography to assess left ventricular function in accordance with standard practice and recommended guidelines if they present with an NSTEMI. All other patients will have an echocardiogram within 24hours of angiogram if one has not been done in the last 12months.

Prior to undergoing coronary angiography 60mls of blood will be taken at the time of angiography for troponin, CK, CKMB, renal function, FBC as is normal practice for patients undergoing angiography. Biomarker evaluation as detailed above will then be performed and the remaining blood will also be frozen at -80C. Assays will be performed in the laboratory of Dr Andrew Wilson (DOM).

All patients will have OCT (St Jude Medical, Westford, MA, USA) in the culprit and non culprit arteries. An OCT catheter will be placed distal to the culprit lesion and pulled back to the proximal part of the vessel using a motorised pullback system. An occlusion balloon will be advanced proximal to the lesion, inflated and saline infused into the coronary artery from the distal tip of the occlusion balloon catheter during image acquisition.

All patients will then have an index of microvascular resistance calculated prior to stenting and then following stent deployment. Briefly the procedure involves:

1) A 0.014 inch coronary pressure wire (RADI Medical systems, Uppsala,

Sweden) is calibrated outside the body, equalised to the pressure reading from the guide catheter with the pressure sensor positioned at the ostium of the guide catheter and then advanced into the distal two-thirds of the culprit vessel.

2) The IMR is then calculated. 3mls of room-temperature saline is injected down the culprit vessel 3 times at rest and the resting transit times, which are inversely proportional to flow, are calculated.

3) Maximal hyperaemia is then induced using intravenous adenosine

4) 3 mls of room temperature saline is then injected down the culprit vessel and hyperaemic transit times recorded

5) Mean aortic and distal coronary pressures are recorded during peak hyperaemia.

6) IMR is then defined as mean distal coronary pressure divided by the inverse of the hyperaemic transit time.

The use of OCT and pressure wires are considered part of standard interventional cardiology practice and are both TGA approved. However, in this study, although there may be instances whereby the RADI wire or an OCT examination is necessary, in the majority of cases we will be using OCT and the RADI wire as research tools. The coronary pressure wire will be used for any intervention performed – this will minimize excessive instrumentation of the coronary arteries. We will also perform IMR assessments on non-culprit vessels. In addition, IMR will be performed in the culprit vessel post stenting. This will allow direct comparison of IMR to see if there has been any microvascular dysfunction as a direct result of the PCI. The performance of IMR and OCT will be expected to add on approximately 45 minutes to the usual procedure. This will not impact upon the patient in any way as any patient having a PCI remains in hospital overnight.

An estimate of mean pre and post PCI values of IMR was obtained from previous studies and based on these, the SD of the IMR measure is 7. We estimated that at least 20 patients should be included in each group to detect a difference in IMR between the two groups that we feel will be clinically relevant.

Patients will stay overnight in-hospital post PCI as is standard practice. Blood samples will be collected 3, 12 and 24 hours post PCI. These samples will be analysed for CK, troponin and inflammatory specific blood markers. The blood samples will undergo normal routine processing and analyses on-site, this currently occurs for all patients undergoing PCI. In addition these blood samples will also be stored (frozen at

-80C) and sent to St Vincent's Hospital for further analysis of inflammatory markers in the laboratory of Dr Andrew Wilson (DOM). It is expected patients in this study will undergo only three extra venepunctures to satisfy blood sampling requirements for this study. However where possible blood will be taken from devices already inserted such as IV cannulas and arterial lines

The primary outcome measure will be frequency of peri-procedural MI in each arm. Secondary outcome measures will be the effect of colchicine on IMR and on inflammatory blood markers.

We used the ESC/ACCF/AHA/WHF "Third Universal Definitions of Myocardial Infarction" to define peri-procedural myocardial infarction (MI type 4a)

Follow-up will be as per usual practice: Patients are reviewed by their referring Cardiologist within 30days of the PCI. This study does not require extra follow-up.

Inclusion Criteria:

1. Male or female over 18 years old
2. Large caliber vessels requiring PCI (>2.5mm diameter vessels)
3. Stable coronary artery disease (CAD) patients: symptomatic patients with stable angina and asymptomatic patients with positive functional tests and obstruction coronary artery disease (defined as diameter stenosis >50%): usually elective patients requiring PCI.
4. NSTEMI (Non ST elevation myocardial infarction) patients (defined as recent onset of chest pain associated with ST segment and/or T wave ECG changes and/or positive cardiac enzymes (creatinine kinase or troponin) with positive functional tests and obstruction coronary artery disease (defined as diameter stenosis >50%)
5. Troponin and CK must have peaked and stabilised prior to PCI
6. On Statin and DAPT

Exclusion Criteria:

1. Cardiogenic shock or Haemodynamic instability
2. ST elevation myocardial infarction
3. Patients who do not go on to have a PCI &/or patients who have a PCI immediately prior to coronary artery bypass grafting
4. AMI with the last 12 months
5. Left main PCI or left main >50% stenosis
6. Chronic total occlusion of a vessel requiring PCI
7. PCI to a small caliber vessel (<2.5mm in diameter), distal vessel, or vessel supplying small distal territory
8. Significant complex disease as deemed by interventionalist
9. Pregnant females or lactating females (Therefore females aged 18 – 45yo @ risk of pregnancy)
10. Less than 18yo

11. Already on colchicine
12. Known hypersensitivity to colchicine
13. Non-compliance to medications
14. Patients not on or unable to take dual anti-platelet therapy or statins
15. Moderate renal impairment defined as creatinine clearance <45ml/min
16. Hepatic dysfunction defined as alanine aminotransferase 1.5 x upper limit of normal range
17. Thrombocytopenia or leukopenia
18. Already on moderate - strong CYP3A4 inhibitors
19. Those with evidence of active infection or inflammatory conditions that might be associated with markedly elevated CRP levels or other inflammatory markers in the blood (eg. active rheumatoid arthritis) and those taking anti-inflammatory therapies (eg. corticosteroids)

Statistical analysis:
Non-normally distributed data will undergo log transformation prior to any statistical test performed. Pearson correlations and independent sample t-tests will be performed on normally distributed data. Spearman correlations and Mann-Whitney tests will be performed on non-normally distributed data.

Conclusion
This project will use a novel method of invasive assessment of the microcirculation to look at microvascular dysfunction in patients undergoing PCI. With the use of IMR, OCT, inflammatory blood markers and markers of platelet activation, we will develop a better understanding on the role of microvascular dysfunction in the development of myocardial infarction. The effect of colchicine on inflammation and microvascular dysfunction will also be examined. Early awareness of MCD at the time of initial percutaneous coronary intervention may promote increasing physician awareness on future prognosis and may warrant a more aggressive treatment strategy.

References

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1.15 Registration and Reporting

(a) If your study is a clinical trial (see 'Module One Guidelines' for definition), is the trial registered with a clinical trials register that fulfils the ICMJE criteria?

Yes ☐ No X Study not a clinical trial **X**

If *Yes*, please provide the name of the register, date of the registration and indicate who undertook the registration:

Name of register: _____

Date of registration:_____

Researcher ☐
Sponsor ☐
Other ☐ Provide details:_____

Please provide the registration number (if known): _____

If you answered *No* to 1.15(a), please justify your response in detail.

This is a sub-component of previously approved project. The addition of colchicine to the current study is a pilot, proof-of-concept study that will form the basis for future larger randomised clinical trial.

(b) Are there any limitations or restrictions on the publication of results by researchers?

Yes ☐ No X

If *Yes*, explain the nature of the limitations or restrictions.

(c) Will a report of the project outcomes (for example, group data) be publicly accessible at the end of the project?

Yes X No ☐

If *Yes*, give details of the type of report and how it will be made available.

If *No*, explain why not.

This is an observational study and the data will be non-identifiable. Data will be submitted to a peer reviewed journal once collected and analysed.

(d) Will a plain English summary of the project outcomes (for example, individual or group data) be made directly available to participants at the end of the project?

Yes ☐ No X N/A ☐

If *Yes*, give details of the type of report and how it will be made available.

If *No*, explain why not.

There will be no group outcomes per se since this is an observational study only.

1.16 Adverse or Unforeseen Events

What procedures are in place to manage, monitor and report adverse and unforeseen events? Consider adverse events in relation to all aspects of the project, including (where applicable) participants, researchers and management of information.

This is not an intervention study so unforeseen and adverse events are generally unexpected. Most of the data will be collected as part of routine clinical care but any adverse events reported to the HREC within 24 hours. However adverse events are extremely uncommon. There are innate risks involved to patients undergoing coronary angiography but this is only being performed in patients where it is clinically indicated and so therefore, there are no significant added

risks with our study protocol. Colchicine is commonly used for various clinical conditions and its side effect profiles are well documented. The low-dose colchicine used in previous similar trials was generally well tolerated and the most common adverse effects were gastrointestinal symptoms. Events relating to management of information will also be reported to the HREC within 24 hours.

SECTION D: PARTICIPANTS

Researchers should consult the Guidelines under Section D for a definition of "participant" for the purposes of this application.

If the project does NOT involve participants, do NOT complete this section, but go directly to Section E. If you are not completing Section D, you may delete it from your application to avoid unnecessary paper usage.

1.17 Number of participants

(a) Total number of participants in the project (at all sites combined)

40

(b) Break down the number of participants for each site for which this HREC is responsible

Site	No. of participants
SVHM	20
Frankston Hospital	20

(c) If the project involves more than one project group (e.g. control and experimental groups), how many participants will be in each group?

1.18 Participants - Details

(a) What categories of people will be recruited? *(e.g. cancer patients, children, people with learning disabilities, pensioners, etc)*

Patients >18yrs old who are awaiting coronary angiography and stenting, and able to provide informed consent.

(b) Will Aboriginal and Torres Strait Islander people be targeted for recruitment to this project?

☐ Yes X No

If *No*, are people of Aboriginal and Torres Strait Islander origin likely to be significantly represented in the cohort of participants recruited?

☐ Yes X No

(c) What will be the age range of participants?

No prespecified range however expected range between 30 and 80

(d) What ethical issues do the criteria for inclusion or exclusion give rise to?

There are no specific issues related to this since the inclusion is very broad.

1.19 Recruitment of Participants

(a) Describe the procedure for recruitment of participants. Include information about

- Source of participants
- Exactly how potential participants will be identified
- Exactly how potential participants will be contacted and by whom, including whether the person making initial contact has any relationship to potential participants
- The method(s) by which information is provided to potential participants (*e.g. verbally, information sheet, fliers, posters, etc*)
- The setting in which information is provided (*e.g. over the telephone, in a clinic or doctor's surgery, through the mail, etc*)

Patients will be recruited from the pre-admission unit and/or coronary care unit. Verbal and written information will be provided to the patient and they will have adequate time (approx 1 hour) to read information provided and ask questions. In routine clinical practice, very little time is allocated for patient consent – at most 30 minutes. Therefore, we feel the provision of 1 hour will be more than enough to go through the study protocol. Patients with ACS or a chest pain syndrome who are scheduled to undergo coronary angiography will be eligible for inclusion. Exclusion criteria include patients unable to give consent, advanced malignancy, and/or acute inflammatory disease.

(b) Will any follow-up procedures be used to improve the rate of participation?

Yes ☐ No X

If *Yes*, describe the procedures.

(c) Will any dependent or unequal relationship exist between anyone involved in the recruitment and the potential participants (e.g. counsellor/client, teacher/student, doctor/patient, warder/prisoner, etc)?

Yes ☐ No X

If *Yes*:

(i) What is the nature of the dependent or unequal relationship?

(ii) How will ethical issues arising from the unequal relationship be addressed?

(d) Will a dual relationship exist between any researcher and participants (e.g. will any of the researchers also be responsible for project, program or administrative oversight within the organisation where it is proposed to recruit participants and carry out the research)?

Yes No X

If *Yes*:

(i) What is the nature of the dual relationship?

(ii) How will ethical issues arising from the dual relationship be addressed?

(e) Will reimbursement, payment or other offers be made to participants?

Yes ☐ No X

If *Yes*, provide details.

1.20 Information to Participants

(a) Does the project design involve deliberate deception of participants?

Yes ☐ No X

If *Yes*, explain why the real purpose of the research needs to be concealed.

(b) Will information about the project be given to participants in the form of a **written** Participant Information?

Yes X No ☐

If *No*, give reasons.

1.21 Consent

(a) Will any of the participants have the capacity to give voluntary and informed consent? Yes X No ☐

If *Yes*, how will consent be obtained?

X Written consent form

☐ Verbal – explain below how consent will be recorded

☐ Implied consent (*e.g. by completing a questionnaire*) – give details

(b) Will any of the participants **not** have the capacity to give voluntary and informed consent? Yes ☐ No X

If *Yes*, who will be asked to provide consent *(tick as many as apply)*?

☐ Parent/guardian

☐ Person responsible (as defined by the *Guardianship and Administration Act* 1986)

☐ Procedural authorisation (as defined by the *Guardianship and Administration Act 1986*). ***Please make sure you also answer question 1.21d below***

☐ Other – give details

How will consent be obtained?

☐ Written consent form

☐ Verbal – explain below how consent will be recorded

(c) How will competence to give consent be determined and who will make this determination?

Patients will already have consented to angiography and stenting.

(d) If this research project is likely to involve procedural authorisation (see question 1.21(b) above), provide details of the following:

- Justify the potential use of procedural authorisation in the research project - that is, provide details regarding how this research project may satisfy the requirements for procedural authorisation;
- Provide details of the steps to be taken to identify and contact a 'person responsible' prior to, and following, the use of procedural authorisation.

N/A

ATTACH A COPY OF PARTICIPANT INFORMATION AND CONSENT FORM(S) AT THE END OF MODULE ONE.

1.22 Consequences of Participation

(a) What are the potential or actual harms of participation (if any)?

The risks will be virtually the same as having the angiogram and stent procedure that the treating physicians feel is clinically indicated and so there is very little added risk beyond this. We will be performing femoral vein cannulation as well as the standard radial/femoral arterial cannulation for the purposes of administering Adenosine in order to achieve maximal hyperaemia. Femoral vein cannulation again carries a small (<1%) risk of haemotoma, infection, deep vein thrombosis and aterio-venous fistula formation to the patient beyond that of the standard angiogram. Adenosine, given during the angiogram is a very safe drug and commonly used in interventional cardiology in the evaluation of intermediate lesions. It can cause facial flushing, headache, shortness of breath, chest pressure, hyperventilation, lightheadedness and dizziness. Such affects are only transient and last no longer than 10 seconds, a result of the short half-life of Adenosine. Blood will be taken from the arterial sheath inserted at the time of angiography and so there will be no pain/discomfort felt by the patient. The collection of urine from the patient will not cause any harm/discomfort to the patient. There is a small increased risk of gastrointestinal symptoms (diarrhea

and nausea) in patients who receive colchicine but the dose we will be using in this study is considerably low.

(b) Is there any possibility of inconvenience to participants?

Yes No X

If *Yes*, please describe.

(c) Is there a need for special counselling?

Yes ☐ No X

If *Yes*, describe the form of the counselling: how it will be conducted, when and by whom?

(d) Will participants be denied access to other treatments, therapies or services as a result of participation? Yes ☐ No X

Give details.

(e) Are there any potential benefits to the participants?

Knowledge of microvascular circulatory function may improve treatment strategies for patients. More intensive cardiovascular evaluation and treatment strategies may reduce the risk of adverse cardiovascular outcomes.

1.23 Other Ethical Issues

Does the project present any other ethical issues with respect to participation? *(e.g. Issues related to illegal activities; indigenous or other special community or cultural groups; risks to third parties, collectivities; etc)*

No

SECTION E: COLLECTION/USE/DISCLOSURE OF INFORMATION

Researchers have a legal as well as an ethical obligation to consider privacy issues. The following questions assist both the researcher and the HREC to fulfil their obligations under State and Commonwealth privacy legislation.

You may delete questions or parts of questions that you are not required to answer, in the interests of reducing paper usage.

1.24 Collection of Information Directly from Individuals

(a) Does the project involve collection of information directly from individuals about themselves?

☐ No - **go to Question 1.25**

X Yes – answer the following questions:

(b) What type of information will be collected? (*Tick as many as apply*)

☐ personal information

☐ sensitive information

X health information

(c) Will participants' consent be sought to use the collected information for

X this research project (specific consent)

X future research related to this project (extended consent)

☐ any future research (unspecified consent)

(d) Does the project involve the establishment of a databank?

X Yes

☐ No

(c) Does the Participant Information and Consent Form explain the following:

The identity of the organisation collecting the information and how to contact it?	YesX No☐
The purposes for which the information is being collected?	YesX No☐
The period for which the records relating to the participant will be kept?	YesX No☐
The steps taken to ensure confidentiality and secure storage of data?	YesX No☐
The types of individuals or organisations to which your organisation usually discloses information of this kind?	YesX No☐
How privacy will be protected in any publication of the information?	YesX No☐
The fact that the individual may access that information?	YesX No
Any law that requires the particular information to be collected?	YesX No

The consequences (if any) for the individual if all or part of the information is not provided Yes X No

If you answered "*No*" to any of these questions, give the reasons why this information has not been included in the Participant Information and Consent Form.

1.25 Do Other Questions in this Section have to be Completed?

(a) Does the project involve the collection, use or disclosure of **identified or potentially identifiable** information from sources other than the individual whose information it is? *(see Module One Guidelines for definitions)*

No – **Go to Question 1.30 and do not answer the remainder of question 1.25, 1.26, 1.27, 1.28 or 1.29**

X Yes – **answer the following question**

(b) Does the project involve the collection, use or disclosure of information **without the consent** of the individual whose information it is (or their legal guardian)?

X No – **Go to Question 1.30 and do not answer questions 1.26, 1.27, 1.28 or 1.29**

☐ Yes – **answer the following questions**

1.26 Type of Activity Proposed

Are you seeking approval from this HREC for

(a) collection of information from a third party?

☐ Yes – **answer Question 1.27**

☐ No – **skip Question 1.27**

(b) use of information?

☐ Yes – **answer Question 1.28**

☐ No – **skip Question 1.28**

(c) disclosure of information?

☐ Yes – **answer Question 1.29**

☐ No – **skip Question 1.29**

If you have answered 'No' to all three parts of Question 1.26, then go directly to Question 1.30

1.27 Collection of Information from a Third Party

Only answer this question if the project involves the collection of identified (or potentially identifiable) information from a source other than the individual (or their legal guardian) without the consent of the individual or their legal guardian.

(a) From which of the following sources will information be collected? *(Tick as many as apply)*

	Source of Information
☐	A Victorian public health service provider
☐	A Victorian private health service provider
☐	An organisation other than a health service provider
☐	A data set under the auspices of the Victorian DHS
☐	A data set under the auspices of another Victorian government department
☐	A data set from another Victorian source
☐	A Commonwealth agency
☐	An agency from another state
☐	An "organisation" as defined in s95A of the Privacy Act
☐	An individual (such as a carer)
☐	Other

List the categories of individuals or organisations from which information will be collected. If information will be collected from more than one category, indicate clearly what information or records will be collected from each category.

Category	**Type of information or records to be collected**
e.g. carers; hospitals	*e.g. contact information; complete medical history*

(b) Have all organisations from which the information is to be collected agreed to provide the information or to allow access to the information?

☐ Yes ☐ No

If *Yes*, provide evidence of this agreement. Provide details of any conditions imposed by the organisation(s) concerning the release of the information.

If *No*, explain how and when the agreement of the disclosing organisation will be obtained.

(c) Is any organisation from which the information will be collected seeking separate HREC approval for disclosure of the information? *(See the Module One Guidelines for further explanation of this question. Note: The organisation(s) disclosing the information is not required by law to obtain separate HREC approval to disclose the information. However, some institutions may wish to obtain separate approval for disclosure for their own purposes.)*

☐ Yes – supply a copy of the decision from the other HREC (when available)

☐ No - a copy of any approval from this HREC will have to be forwarded to the disclosing organisation

(d) Does the person who is collecting the information routinely have access to that information?

☐ Yes ☐ No

(e) What information will be collected? (*Tick all boxes that apply*)

	Type of information		**Type of organisation(s) involved**	**Privacy Principle(s)**
☐	Health information	☐	Victorian public sector	HPP 1
		☐	Victorian private sector	HPP 1, NPP 1, NPP 10
		☐	Commonwealth public sector	IPP 11
		☐	Other	NPP 1, NPP 10
☐	Personal information (other than health information)	☐	Victorian public sector	VIPP 1
		☐	Victorian private sector	NPP 1
		☐	Commonwealth public sector	IPP 11
		☐	Other	NPP 1
☐	Sensitive information	☐	Victorian public sector	VIPP 10
		☐	Victorian private sector	NPP 10
		☐	Commonwealth public sector	IPP 11
		☐	Other	NPP 10

(f) Give reasons why information will not be collected in a de-identified form.

(g) For what reason(s) will consent not be obtained from the individual(s) whose information will be collected?

(h) Give reasons why the proposed collection of information is in the public interest. Note that the public interest in the proposed research must substantially outweigh the public interest in respecting individual privacy.

1.28 Use of Information

Only answer this question if the project involves the use of identified (or potentially identifiable) information without the consent of the individual whose information it is (or their legal guardian).

(a) What information will be used? (*Tick all boxes that apply*)

	Type of information		**Type of organisation(s) involved**	**Privacy Principle(s)**
☐	Health information	☐	Victorian public sector	HPP 2
		☐	Victorian private sector	HPP 2, NPP 2
		☐	Commonwealth public sector	IPP 11
		☐	Other	NPP 2
☐	Personal information (other than health information)	☐	Victorian public sector	VIPP 2
		☐	Victorian private sector	NPP 2
		☐	Commonwealth public sector	IPP 11
		☐	Other	NPP 2
☐	Sensitive information	☐	Victorian public sector	VIPP 2
		☐	Victorian private sector	NPP 2
		☐	Commonwealth public sector	IPP 11
		☐	Other	NPP 2

(b) What are the specific purposes for which the information will be used?

(c) Is the purpose for which the information will be used (the secondary purpose) related to the purpose for which the information was **originally** collected (the primary purpose)?

☐ Yes ☐ No

Give details.

(d) Give reasons why information will not be used in a de-identified form. *(If the answer is the same as for Q1.27 (f), write "as above".)*

(e) For what reason(s) will consent not be obtained from the individual(s) whose information will be used? *(If the answer is the same as for Q1.27 (g), write "as above".)*

(f) Give reasons why the proposed use of information is in the public interest. Note that the public interest in the proposed research must substantially outweigh the public interest in respecting individual privacy. *(If the answer is the same as for Q1.27 (h), write "as above".)*

1.29 Disclosure of Information

Only answer this question if the project involves the disclosure of identified (or potentially identifiable) information without the consent of the individual whose information it is (or their legal guardian).

(a) Will identified (or potentially identifiable) information be disclosed by an organisation to the researcher?

☐ No – **Go to question 1.29(b)**

☐ Yes – answer the following question

What information will be disclosed by the organisation(s) to the researcher? (*Tick all boxes that apply*)

	Type of information		**Type of organisation(s) involved**	**Privacy Principle(s)**
☐	Health information	☐	Victorian public sector	HPP 2
		☐	Victorian private sector	HPP 2, NPP 2

		☐	Commonwealth public sector	IPP 11
		☐	Other	NPP 2
☐	Personal information (other than health information)	☐	Victorian public sector	VIPP 2
		☐	Victorian private sector	NPP 2
		☐	Commonwealth public sector	IPP 11
		☐	Other	NPP 2
☐	Sensitive information	☐	Victorian public sector	VIPP 2
		☐	Victorian private sector	NPP 2
		☐	Commonwealth public sector	IPP 11
		☐	Other	NPP 2

List the organisations that will disclose information to the researcher. If more than one organisation is involved, indicate clearly what information or records will be disclosed by each organisation to the researcher.

(b) Will identified (or potentially identifiable) information be disclosed by the researcher to other organisations?

☐ No – **Go to question 1.30**

☐ Yes – answer the following questions

What information will be disclosed by the researcher? (*Tick all boxes that apply*)

	Type of information		**Type of organisation(s) involved**	**Privacy Principle(s)**
☐	Health information	☐	Victorian public sector	HPP 2
		☐	Victorian private sector	HPP 2, NPP 2
		☐	Commonwealth public sector	IPP 11
		☐	Other	NPP 2
☐	Personal information (other than health information)	☐	Victorian public sector	VIPP 2
		☐	Victorian private sector	NPP 2
		☐	Commonwealth public sector	IPP 11
		☐	Other	NPP 2
☐	Sensitive information	☐	Victorian public sector	VIPP 2
		☐	Victorian private sector	NPP 2
		☐	Commonwealth public sector	IPP 11
		☐	Other	NPP 2

List the organisations to which information will be disclosed. If information will be

disclosed to more than one organisation, indicate clearly what information or records will be disclosed in each case.

(c) Give reasons why information will not be disclosed in a de-identified form. *(If the answer is the same as for Q1.27 (f) or Q1.28 (d), write "as above".)*

(d) For what reason(s) will consent not be obtained from the individual(s) whose information will be disclosed? *(If the answer is the same as for Q1.27 (g) or Q1.28 (e), write "as above".)*

(e) Give reasons why the proposed disclosure of information is in the public interest. Note that the public interest in the proposed research must substantially outweigh the public interest in respecting individual privacy. *(If the answer is the same as for Q1.27 (h) or Q1.28 (f), write "as above".)*

1.30 General Issues

(a) How many records will be collected, used or disclosed? Specify the information that will be collected, used or disclosed *(e.g. date of birth, medical history, number of convictions, etc)*

Number of records: 40 **Type of information:** medical history, date of birth

(b) Does the project involve the adoption of unique identifiers assigned to individuals by other agencies or organisations?

☐ Yes X No

If *Yes*, give details of how this will be carried out in accordance with relevant Privacy Principles (e.g. HPP 7, VIPP 7 or NPP 7).

(c) Does the project involve trans-border (i.e. interstate or overseas) data flow?

☐ Yes X No

If *Yes*, give details of how this will be carried out in accordance with relevant Privacy Principles (e.g. HPP 9, VIPP 9 or NPP 9).

(d) For what period of time will the information be retained? How will the information be disposed of at the end of this period?

15 years

(e) Describe the security arrangements for storage of the information. Where will the information be stored? Who will have access to the information?

Password protected database. PIs and CIs only will be able to access data.

(f) How will the privacy of individuals be respected in any publication arising from this project?

All data will be non-identifiable

1.31 Other Ethical Issues

Discuss any other ethical issues **relevant to the collection, use or disclosure of information** proposed in this project. Explain how these issues have been addressed.

SECTION F: FINANCIAL AND RELATED ISSUES

1.32 Potential Conflict of Interest

Do any researchers have any financial interests in this research or its outcomes, or any relevant affiliations?

Yes ☐ No X

If *Yes*, give details

If you have declared a potential conflict of interest, you should include an appropriate comment on the Participant Information and Consent Form.

1.33 Indirect Costs

Will there be payments over and above the direct costs of this project (e.g. conference and travel, recruitment incentives, equipment)?

Yes ☐ No X

If *Yes*, please provide details of payments and justification for them.

1.34 Project Budget

Attach a detailed project budget to this application.

Have you included:

- Salaries with on-costs ☐
- Administration costs ☐
- Research consumables (for example, bed-day costs) ☐
- Participant reimbursement ☐
- Departmental charges (e.g. Pharmacy, Pathology, Radiology) ☐

If a detailed budget is not being provided, give reasons.

This is not a commercial study and most of the data is collected as part of routine clinical care. All salaries are already provided as existing members of staff. Most testing is part of routine clinical care.

Cost of pressure wires (RADI) – $11,000 – many wires will be used as part of normal clinical practice and therefore won't add to the cost of the project.

Specific Blood Tests costing are as follows:

SCD40 ligand - $10 per patient

SRAGE - $20 p/p

HsCRP - $20 p/p

Approximate costing for all specific blood testing will be $14400

1.35 Source of Funding

How will this project be funded? List all sources of funds (*e.g. commercial sponsorship, grant, departmental funds etc*).

Source	Amount in $	Status of Funds	
		Application pending	**Funds Available**
Departmental funding	20,000		X
NHMRC Grant Jamie Layland	5,000		X

1.36 Funds Coverage

Do the funds presently available or applied for cover all requirements to conduct the project?

Yes X No ☐

If *No*, explain how the shortfall will be made up or dealt with.

1.37 Claims through Medicare

Will any charges be incurred by Medicare as a result of patient screening or participation?

Yes ☐ No X N/A

If *Yes*, has the Health Insurance Commission been notified and have they given permission?

Yes ☐ No ☐

1.38 Declaration by Researchers

Project Title: Physiology of Acute Coronary Syndromes : Focus on inflammation and microvascular dysfunction.

I/WE, the researcher(s) agree:

- To only start this research project after obtaining final approval from the Institution's Human Research Ethics Committee (HREC);
- To conduct this research project in accordance with the protocols and procedures as approved by the HREC;
- To only carry out this research project where adequate funding is available to enable the project to be carried out according to good research practice and in an ethical manner;
- To provide additional information as requested by the HREC;
- To provide progress reports to the HREC as requested, including a final report and a copy of any published material at the end of the research project;
- To maintain the confidentiality of all data collected from or about project participants;
- To notify the HREC in writing immediately if any change to the project is proposed and await approval before proceeding with the proposed change;
- To notify the HREC in writing immediately if any adverse event occurs after the approval of the HREC has been obtained;
- To agree to an audit if requested by the HREC;
- To only use data and any tissue samples collected for the study for which approval has been given;
- To only grant access to data to authorised persons; and
- To maintain security procedures for the protection of privacy, including (but not restricted to): removal of identifying information from data collection forms and computer files, storage of linkage codes in a locked cabinet and password control for access to identified data on computer files.

I/we have read the NH&MRC *National Statement on Ethical Conduct in Research Involving Humans* 1999 and will observe the principles set out in that document and in the *Declaration of Helsinki*.

Name of principal researcher .....
Signature Date

Name of researcher …….

Signature Date

Name of researcher …….

Signature Date

1.39 Certification by Principal Researcher and Head of Department

Project Title:

Certification By Principal Researcher

I accept responsibility for the conduct of this research project according to the principles of the *National Statement on Ethical Conduct in Research Involving Humans* published by the National Health & Medical Research Council (June 1999).

I certify that all researchers and other personnel involved in this project are appropriately qualified and experienced or will undergo appropriate training to fulfil their role in this project.

As principal researcher, I will take responsibility for the confidential maintenance of records for 7 years after completion of the project (15 years in the case of drug trials).

Name of principal researcher: …….

Signature Date

Acceptance by Head of Department/Divisional Director/Authorised Institutional Official*

I certify that I have read the research project application named above.

My signature indicates that I support this research project.

Name of Head of Department (or appropriate person): ……

Name of Department (or relevant section): ……

Signature Date

*Where an investigator is also Head of Department, certification must be sought from the person to whom the Head of Department is responsible. Investigators, who are also Department Heads or Divisional Directors, must not approve their own research on behalf of the Institution.

1.40 Declaration by Head of Supporting Department

This form is to be completed by the Head of any Department that is providing support or services to the research project, but which does not have any member(s) on the research team.

If completing this form by hand, please use BLACK INK only.

Project Title:
Principal Researcher:

I have discussed this project with the Principal Investigator and have seen the application and protocol. I am (*tick whichever applies*)

☐ able to perform the investigations/services indicated, within the present resources of the Department;

☐ able to perform the investigations/services indicated, if the following financial assistance is provided:

☐ unable to undertake the investigations/services indicated, on the following grounds:

Name: …….

Signature: …….. Date:

Head of the Department of ……

MODULE ONE: CHECKLIST

Please satisfy each of the following before submitting the application. Failure to do so will delay review of the application.

Include a copy of this checklist (completed & signed) with the application.

Full Project Title

Physiology of Acute Coronary Syndromes: Focus on inflammation and microvascular dysfunction.

Have you answered all relevant questions in Module 1?	☐
Is a staff member from the Institution listed as a co-researcher?	☐
Have you defined all technical terms and abbreviations used?	☐
Have you included all questionnaires or surveys to be used?	☐
Have you completed all financial details in Module 1, Section F?	☐
Have you included a detailed project budget?	☐
Have you declared all potential conflicts of interest?	☐
Have you included any other site-specific modules or documentation specifically required by the Institution(s) at which you intend to conduct your research?	☐
Do the Participant Information and Consent Form(s) show the name of the Institution, with pages numbered & dated in the footer?	☐
Are all relevant modules stapled separately, in order? *Note: Attach attachments for each module at the end of that module*	☐
Are all pages (including attachments) numbered in the footer?	☐
Have you provided an original and the required number of copies?	☐
Have you completed the form "Declaration by Researcher(s)?	☐
Have you completed the form "Certification by Principal Researcher and Head of Department"?	☐
Has a completed "Declaration by Head of Supporting Department" been included for each supporting department (if applicable)?	☐

Name of principal researcher-…….

Signature Date