

# **CVLPRIT Pilot Study**

## **(Complete Versus Lesion-only PPrimary PCI Pilot)**

A study of patients with multi-vessel disease presenting with acute myocardial infarction undergoing primary percutaneous coronary intervention (PPCI) including a prospective registry of all PPCI patients, and a pilot study in a subset of patients with multi-vessel coronary disease randomised to a strategy of early multi-vessel revascularisation or infarct related artery revascularisation only

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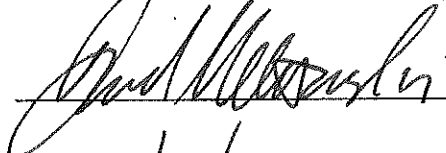
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### 3. ABBREVIATIONS

ACS	Acute coronary syndrome
CABG	Coronary artery bypass grafting
CCS	Canadian Cardiovascular Society
CERC	Clinical Events Review Committee
CKMB	Creatine kinase myocardial brain
CMR	Cardiac Magnetic Resonance Imaging
CTEU	Clinical Trials and Evaluation Unit
ECG	Electrocardiogram
CRF	Case record form
FBC	Full blood count
GCP	Good Clinical Practice
HAC	Heart Attack Centre
IRA	Infarct related artery
LBBB	Left Bundle Branch Block
MI	Myocardial infarction
MPS	Myocardial Perfusion Scan
MRIS	Medical Research Information System
MVD	Multi-vessel disease
MVT	Multi-vessel treatment
N-IRA	Non-infarct related epicardial coronary artery
Non STEACS	Non ST elevation acute coronary syndrome
NSTEMI	Non ST elevation myocardial infarction
PPCI	Primary percutaneous coronary intervention
PCI	Percutaneous coronary intervention
RCT	Randomised Controlled Trial
STEMI	ST elevation myocardial infarction
U & E	Urea and Electrolytes
TSC	Trial Steering Committee

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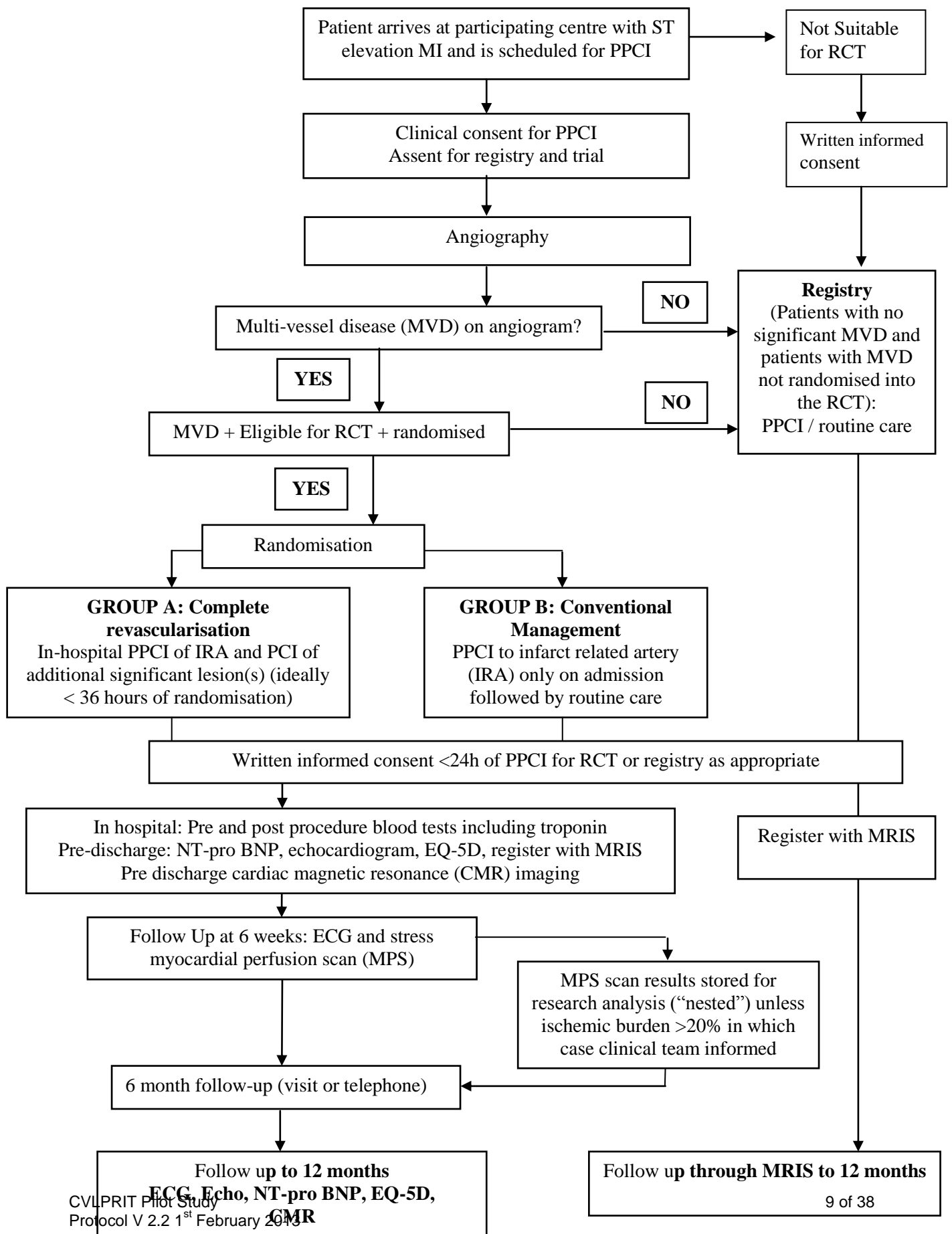
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#### 4. TABLE 1: CVLPRIT TRIAL SUMMARY

<b>Title</b>	Complete Versus Lesion-only Primary PCI Pilot Study
<b>Acronym</b>	CVLPRIT
<b>Study Design</b>	Prospective observational registry and open multi-centre randomised controlled trial (RCT) in a subset of patients with multi-vessel coronary artery disease
<b>Registry</b>	All patients presenting for PPCI and not included in the RCT: collect demographics and in-hospital data
<b>Registry sample size and follow-up</b>	<ul style="list-style-type: none"> <li>Estimated sample size 1000 patients</li> <li>Registered with MRIS for follow-up to 12 months for vital status and up to 20 years</li> </ul>
<b>Randomised controlled trial (RCT) Eligibility</b>	<p><b>Inclusion</b></p> <ul style="list-style-type: none"> <li>Suspected or proven acute myocardial infarction</li> <li>Significant ST elevation or left bundle branch block (LBBB) on ECG (in cases of LBBB, angiographic confirmation of IRA occlusion is required)</li> <li>&lt; 12 hrs of symptom onset</li> <li>Scheduled for Primary PCI for clinical reasons</li> <li>Provision of verbal assent followed by written informed consent</li> <li>Multi-vessel coronary artery disease at angiography defined as: Infarct related artery (IRA) plus at least one non-infarct related epicardial artery (N-IRA) with at least one lesion deemed angiographically significant (&gt;70% diameter stenosis in one plane). The N-IRA should be a major (&gt;2mm) epicardial coronary artery or branch (&gt;2mm) and be suitable for stent implantation.</li> </ul> <p><b>Exclusion</b></p> <ul style="list-style-type: none"> <li>Any exclusion criteria for PPCI</li> <li>&lt; 18 years age</li> <li>Clear indication for, or contraindication to, multi vessel PPCI according to operator judgement</li> <li>Previous Q wave myocardial infarction</li> <li>Patients with prior CABG</li> <li>Cardiogenic Shock</li> <li>VSD or moderate/severe mitral regurgitation</li> <li>Chronic kidney disease (Cr&gt;200µmol/l or eGFR&lt;30ml/min)</li> <li>Suspected or confirmed thrombosis of a previously stented artery Where the only significant N-IRA lesion is a chronic total occlusion (CTO)</li> </ul>
<b>RCT Randomisation</b>	<p>Group A: In-patient total coronary revascularisation - <u>preferably</u> IRA + then non -IRA within 36 hours</p> <p>Group B: IRA revascularisation <u>only</u> at admission PPCI</p>
<b>RCT Recruitment, sample size and Follow up</b>	<ul style="list-style-type: none"> <li>7 centres recruiting 300 patients over 9 - 24 months</li> <li>Need for further invasive management will be determined by ischaemic symptoms at any time during follow-up with confirmation by non-invasive imaging</li> <li>All patients will undergo Myocardial Perfusion Scan at 6 -8 weeks.</li> <li>Clinical follow-up at 6 and 12 months (RCT patients only)</li> <li>Cardiac Magnetic Resonance Imaging (CMRI) facilities available</li> </ul>
<b>RCT Outcome measures</b>	<p>PRIMARY: Cumulative Major Adverse Cardiovascular Events (MACE) [all-cause mortality, recurrent MI, heart failure, need for revascularization (PCI or CABG) up to 12 months]</p> <p>SECONDARY</p> <ol style="list-style-type: none"> <li>Individual components of primary composite outcome</li> <li>Safety: Emergency CABG, Confirmed stroke, Major bleeding, Surgical repair of vascular complications, up to 12 months</li> <li>Number of patients presenting with PPCI with significant MVD</li> <li>Ischaemic burden at 6-8 weeks (expressed as % of total ) by MPS</li> <li>Economic assessment and cost efficacy including days in hospital at 12 months</li> <li>Contrast Induced Nephropathy (rise Cr &gt;25%) or 44.2µmol/l within 48hrs persisting ≥48 hours</li> <li>Change in NT-ProBNP from pre-discharge to 12 months</li> <li>Echocardiographic LVEF and wall motion score (Discharge and 12 Months)</li> <li>Quality of Life Score at 12 Months (EuroQol questionnaire)</li> <li>Infarct size, extent of microvascular obstruction, myocardium salvaged, LV volumes and EF at discharge by CMR and new myocardial injury and volumes at 9-12 months</li> </ol>



## 5. FIGURE 1: CVLPRIT STUDY FLOW DIAGRAM



## 6. LAY ABSTRACT

Patients who present with heart attacks are increasingly treated with balloons and stents to open their blocked arteries (primary percutaneous coronary intervention: PPCI). Mostly patients present with blockage of a single major coronary artery. However if they have an important narrowing in another artery it can be difficult to decide whether this other narrowing should be treated at the same time. There are no reliable studies to tell heart specialists what to do. This study will enrol patients with heart attacks and multiple narrowed arteries, and randomly allocate treatment in two groups. One group will have the blocked (heart attack-causing) artery, plus any other significantly narrowed artery, treated at the same time, while the second group will have only the blocked artery treated. In the second group any other narrowing will be left alone (which is the routine procedure at present) but they will be treated if needed according to symptoms during follow up. The study will determine which strategy (treating all at the first presentation, or treating only the blocked artery and the other artery with the narrowing in it if needed during follow up) has the better outcome at 12 months. A myocardial perfusion scan (used to detect changes in blood flow in the heart) will be undertaken at 6-8 weeks, but the results will only be used to change treatment if the results show severe reduction in blood flow to the heart. Otherwise the scan results will be reviewed at the end of the study to see if the scan could have predicted the 12 month clinical outcome. We also need to find out how many patients present to heart attack centres with an important narrowing in more than one artery and this will be done by maintaining a registry of all patients admitted to the four hospitals taking part with this problem who undergo a PPCI. Additional information about heart function and recovery will be obtained by Cardiac Magnetic Resonance (CMR) imaging scans (measuring the amount of heart muscle scar) in hospital and at one year.

## 7. INTRODUCTION

There are no reliable data to determine the best management of patients with ST elevation Myocardial Infarction (STEMI) presenting for Primary-PCI (PPCI) with multi-vessel disease (MVD). Some registries indicate that all lesions should be treated during the PPCI or within that hospital admission, while others support a deferred post-discharge treatment strategy. Various management strategies exist amongst operators with no certainty as to the most appropriate. As PPCI increasingly becomes the first line reperfusion strategy, this management dilemma will increase. CVLPRIT is a pilot study to determine the incidence of MVD in those presenting for PPCI via a registry of all presenting patients and is also designed to test the feasibility and outcome of randomisation to either complete revascularization (infarct and significant disease in non-infarct related artery) at time of presentation PPCI (or as early as possible during index admission if deemed clinically appropriate to delay treatment at time of admission), or to treatment of the infarct related artery only. CVLPRIT will identify event rates at 12 months and the extent of infarction, reversible ischaemia and long term ventricular function in the two groups. It will also determine the value of interim non-invasive imaging. Outcomes in those with MVD but not randomised into the trial will also be determined through the registry. Recruitment will take place in 4 recognised PPCI centres. **CVLPRIT** will allow for the future design of a robust pivotal trial but importantly itself may indicate the best management of such patients.

### Current Indications and Strategies in Primary PCI

Prompt restoration of coronary blood flow and maintenance of coronary patency are the primary aims of the management of ST-segment elevation myocardial infarction (STEMI), since this limits infarct size, and prolongs survival. Achieving these goals by mechanical means (Primary percutaneous coronary intervention, PPCI), appears to confer short and long-term prognostic benefits compared to in-hospital intravenous thrombolysis.(1, 2) In a 23 trial meta-analysis PPCI reduced the short and long-term risk of death, recurrent MI or stroke compared with in-patient thrombolysis (8% v 14%,  $p < 0.0001$ ). (3) European and U.S. guidelines support PPCI with a Class I indication for use as first-line therapy for STEMI,

providing it can be delivered by an experienced team within mandated guidelines.(4, 5) In the UK current practice for patients presenting with STEMI undergoing PPCI who have multi-vessel disease is that intervention may be performed to clinically important non-infarct lesions (N-IRA) at the time of the initial procedure, or may be deferred to a later, staged PCI procedure, or indefinitely pending non-invasive assessment of ischaemia and /or assessment of the patient's subsequent symptoms. Opinion and practices regarding N-IRA intervention, and importantly its timing, vary because of lack of data. It is these uncertainties that this study programme (initial pilot study followed by a larger definitive pivotal trial) plans to investigate.

### **Primary PCI in the Setting of Multi-vessel Coronary Disease**

The UK has seen a rapid increase in uptake of PPCI. In 2006 the British Cardiovascular Intervention Society audit records 3960 PPCIs out of >73,000 PCIs and >100 000 STEMI hospital admission episodes. According to audit returns procedural success with PPCI was > 90% with a post-infarct in-hospital mortality of 4.6%. PPCI activity is projected to increase further as more PCI centres expand to offer infarct angioplasty: the number of PCI centres providing PPCI rose from 18 in 2004 to 60 of 91 centres in 2007, with 23 running the service 24/7.(6) The National Infarct Angioplasty Project (Oct 2008) promotes the widespread dissemination of PPCI as first line treatment for STEMI (7). However large epidemiological studies suggest at least 30% of patients presenting for initial PPCI angiography have multi-vessel coronary disease, while institutional registries and large randomized trials report multi-vessel disease in 40-50% of patients with STEMI. (8-12)

### **Need for a Randomised Trial comparing interventional strategy at time of PPCI**

Currently there is no consensus on the optimal management of significant 'non-culprit' coronary artery lesions identified at PPCI. Existing data are largely retrospective in nature, and importantly, conflicting. Some clinicians routinely do the "significant-other" during the in-hospital stay, others perform a non invasive test to determine the presence of continuing ischaemia. The best management of non-culprit lesions identified at the time of angiography during PPCI is thus uncertain with significant variations in interventional practice. A report of 11294 patients by Hannan (13) from the New York state PCI showed that rates of freedom from death or MI were 93.3% in patients with "complete" revascularisation (31% of total) compared to 91.7% for those with "incomplete" revascularisation (p=0.002) in a risk adjusted model. In CVLPRIT we will also perform a registry of all patients presenting to participating centres during the study period to determine the incidence of MVD and we will investigate a major adverse cardiovascular (MACE) outcome in those deemed suitable for randomisation to a strategy of in-patient treatment of culprit and non-culprit lesions or in-patient treatment of infarct-related artery PCI only.

### **Rationale for studying the different treatment strategies in CVLPRIT**

Recent attention has focused on the diffuse inflammatory nature of acute coronary syndromes (ACS), including STEMI, with multiple unstable atheromatous plaques detected during periods of coronary instability (14). Thus undertaking multi-vessel PCI in the peri-infarct period may reduce overall ischaemic burden and subsequent post PPCI adverse events by preventing the incidence of both early and late recurrent ischaemia in the non-infarct related lesions, reducing the need for recurrent procedures, and subsequent acute MACE (15). Complete revascularization at the time of infarction may also reduce hospital stay and total care costs. Randomized trial data in stable elective patients suggest complete revascularization improves long-term prognosis in patients with MVD, and that complete revascularization at a single session is associated with similar outcomes to that following staged PCI procedures (16-19). Conversely, concern exists regarding the risks of prolonged procedural infarct PCI and the hypothetical risk of stent thrombosis in N-IRA arteries when stent implantation has taken place in the thrombogenic milieu of STEMI. A successful PPCI to the IRA and a difficult and unsuccessful PCI to the N-IRA would be potentially hazardous especially in the unwell patient. Focusing on the obvious, easily managed, occluded artery may drive operators towards a

simple IRA-only strategy. Thus the optimal strategy for managing multi-vessel disease during STEMI PPCI is unknown.

#### **Available data: Infarct related artery only versus multi-vessel treatment in P-PCI: Why do we need a trial?**

From the Keeley meta-analysis comparing primary PCI with thrombolysis in STEMI, the 1 year death rate among all-comers undergoing PPCI was 10% and the rate of death, myocardial infarction or stroke was 14% (3). These trials however did not specifically address outcomes in the 30% of patients with multi-vessel coronary disease. Among retrospective studies looking at PPCI and the management of multi-vessel CAD, Roe et al found an increase in mortality at 6 months in those with multi-vessel CAD, and treated IRA + N-IRA compared matched controls, and *Corpus* reported a higher rate of adverse events at one year among patients undergoing multi-vessel PCI at time of infarction, driven largely by an increase in need for repeat revascularization (20-21). In both these studies the control group was heterogeneous in terms of timing and indications for management of the N-IRA disease. Conversely five other non-randomized studies broadly support complete revascularization at the time of PPCI. Qarawani et al found a large reduction in recurrent MI and need for revascularization among those undergoing multi-vessel treatment at time of PPCI with similar mortality at one year to culprit-only PCI (22), while studies by Goldstein (14) and Kahn (23) support the safety of multi-vessel treatment at the time of PPCI and furthermore that staged PCI during the same hospital admission resulted in favourable short-term outcomes compared to a strategy of N-IRA medical management or post-discharge ischaemia driven N-IRA PCI. In a review of about 2000 patients in the New York State Angioplasty Registry 2000-2001 patients Kong et al suggested that despite the added complexity of multi-vessel treatment during PPCI, those undergoing complete revascularization during the index admission had significantly lower in-hospital mortality than those with multi-vessel disease treated by IRA-only PPCI (24). Finally, sub-group analysis of the CADILLAC trial suggested the presence of untreated non-infarct related lesions following PPCI independently predicted adverse events at one year (25). None of this data however provides sufficient evidence on which to base clinical practice.

Only three small prospective studies have randomized patients to either complete or 'culprit-only' revascularization during P-PCI. In an echocardiographic study Ochala et al randomized patients with STEMI and multi-vessel disease to 'immediate complete' multi-vessel treatment at time of PPCI or to staged planned in-hospital N-IRA revascularization and found similar recovery of left ventricular function in the two groups (26). The HELP-AMI study (Di Mario et al) enrolled 69 patients and found similar rates of repeat revascularization, new MI or death at 12 months in patients undergoing immediate complete PPCI or culprit-only revascularization with N-IRA management at operator discretion (27). Politi et al in a study of 214 STEMI patients with multi vessel coronary disease scheduled for PPCI randomised to culprit vessel angioplasty-only, staged revascularisation, or simultaneous treatment of non-IRA (28). During a mean follow-up of 2.5 years, the rate of MACE was 50%, 20.0% and 23% respectively ( $p < 0.01$  for difference between culprit only and other groups), but staged and simultaneous multi-vessel revascularisation were not significantly different. As can be seen from Table 1 there is disparity of data and outcomes and thus a clear need for a trial to help guide management. CVLPRIT will help capture important data in a clinical scenario where the optimal management strategy is unclear. It will randomize patients to one of two management strategies mirroring current variations in UK and global practice.

We also propose to evaluate the role of cardiac magnetic resonance imaging in the early post acute phase of STEMI to determine infarct size, ventricular function and volumes and to determine the extent of myocardial salvage 9-12 months later (29). Details are summarised in Appendix 3.

**Expected value of results**

Data from 4 studies comparing culprit-only or complete revascularization in the setting of AMI suggest that 1 year MACE rate in patients with IRA-only PCI at time of AMI may be as high as 40% and the estimated MACE rate in patients undergoing multi-vessel PCI at 30% and this difference is probably driven by the need for repeat re-vascularisation in the IRA-only group (20, 21, 27, 28). The question of early complete revascularisation in patients with multi-vessel disease undergoing PPCI is important as this approach could reduce the risk of future MI /death and prevent the need for repeat PCI. Since the rates of PPCI are increasing in the UK, this issue will only become more important to address. In this programme we propose a two stage evaluation process. The initial pilot phase (present study) to determine the scale of the problem, differences in outcomes between the two randomised strategies, feasibility of enrolment and subsequent burden of residual ischaemia. A second larger study may be needed to determine the clinical efficacy of multi-vessel revascularisation in the setting of PPCI and will also have a careful evaluation of costs and cost effectiveness of the multi-vessel PCI approach. If our programme suggests a benefit from total in-hospital revascularisation, then the need for subsequent revascularisation procedures occurring after discharge, and adverse clinical events like death and myocardial infarction, may be reduced.

**8. Table 2: Published studies comparing culprit-only PCI with multi-vessel treatment (MVT) PCI following ST-segment elevation MI**

TRIAL (REF)	DESIGN	YEAR	MEAN F/U	FAVOURED STRATEGY	FINDINGS	COMMENT
Roe et al (17)	Retrospective with matched controls, n=79	1995-99	6/12	↔	Non-significant trend to increased mortality (25% v 16.4%) with MVT	
Corpus et al (16)	Retrospective, n=820	1998-2002	1 year	<b>IRA only</b>	MACE with MVT 40% v 28%, p=0.006	
Goldstein et al (12)	Retrospective angio review, n=253	2005	1 year	↔	Similar MACE and mortality at one year	Observational angio study
Kahn et al (18)	Retrospective, n=285	1990	In-hospital	↔	57% had multi-vessel disease, no significant difference in outcome with MVT	
Kong et al (20)	Retrospective, n=1982	2000-2001	In-hospital	<b>MVT</b>	Lower in-hospital mortality (0.8% v 2.3%, p=0.018) with MVT despite higher risk profile	
Sorajja et al (21)	Sub-group analysis of CADILLAC trial	1998-2000	1 year	n/a	Presence of untreated non-IRA lesions independently associated with higher MACE, HR 1.80, p=0.0009	Not a pre-specified sub-group, not stratified by PCI strategy
Ochala et al (22)	Randomized trial (immediate complete versus staged MVT), n=136	2003	6/52	↔	Similar improvement in LV function at 6/52 with MVT or IRA-only PCI	Echo data only
Di Mario et al (23)	Randomized controlled trial, n=69	2002	1 year	↔	No MACE difference. Trend to less (17% v 35%, p=0.247) repeat revascularization with MVT. Equivalent costs	Study powered on basis of cost efficacy calculation, unequal randomization
Politi L et al (36)	Randomized trial (immediate complete vs. staged vs. culprit-only) n=214	2005-2008	2.5 yrs	<b>MVT</b>	Significantly lower MACE in both staged and immediate complete groups (20% and 23.1%) versus culprit-only (50%), p<0.001. Driven by repeat revascularization.	Protocol for determining subsequent revascularization poorly defined

## **9. STUDY HYPOTHESIS**

CVLPRIT will be a hypothesis generating pilot study based at seven UK PCI centres (Leicester, Southampton, Harefield, Kettering, Derby, Leeds and Bournemouth). A pragmatic sample size of 150 randomized patients per group will be undertaken with the aim of providing sufficient data to demonstrate the feasibility and safety of PCI to multiple vessels and whether there is likely to be a difference in outcome between the two strategies which could if necessary be tested more robustly in a larger study which could be designed using our findings. CVLPRIT will provide information on timing of in-patient non-culprit lesion PCI and the extent of residual ischaemia as well as initial and longer term clinical outcome data. The centres involved are all experienced interventional centres with experience in clinical trials. The CVLPRIT data will provide information for end points, sample size estimation and secondary outcomes to be measured if a subsequent pivotal trial is needed as well as telling us about MVD in STEMI PPCI in the “real” world.

## **10. AIMS OF THE STUDY**

1. Set up a registry to record demographics and outcomes of patients presenting with STEMI at participating hospitals treated with PPCI over 24 months.
2. Document the proportion of PPCI patients who also have multi-vessel disease.
3. Randomise potentially eligible patients with multi-vessel disease to a strategy of complete in-hospital revascularisation or to treatment of infarct related artery only.
4. Determine the number of patients who present with MVD who are not randomised into the study and importantly document the reasons why not.
5. Document Major Adverse Cardiovascular Events (MACE: all-cause death, recurrent MI, severe heart failure, need for revascularization (PCI or CABG) safety outcomes (emergency CABG, stroke, major bleeding, surgical repair of vascular complications) up to 12 months in those randomised to either strategy, in the Registry of non MVD patients and in those with MVD deemed not suitable for randomisation
6. Compare total infarct size, myocardial salvage, cardiac volumes and ejection fraction pre-discharge and at 9-12 months between the "complete" and "culprit only" revascularisation strategies.
7. Determine the presence and extent of myocardial ischaemia at 6 weeks by myocardial perfusion scans in RCT patients.

## **11. REGISTRY**

One of the key aims of this CVLPRIT pilot study is to determine the numbers of potentially eligible patients and the feasibility of enrolment into the randomised aspect of the study. A register of all patients undergoing PPCI at participating centres will be carried out. On admission all patients will be asked to provide a verbal informed “Assent” to participate in the research protocol study which will including the registry and RCT, this which will be documented in the patients’ hospital records. Assent will be obtained at the same time as clinical consent is taken for PPCI, by appropriately medically qualified personnel. Full written informed consent for registry patients will be obtained <24 hours after PPCI for the recording of simple anonymous data (age, gender, medical history, angiographic results) and follow-up at one year using centralised registers for death and hospital admissions. All patients with MVD will be considered for and approached to be included in the randomised trial.

If a patient is not suitable for RCT, this patient can be approached after the PPCI to include in the REGISTRY. If patient agrees full written informed consent is obtained

The main aims of the registry are:

1. Identify the proportion of those presenting for PPCI who have significant multi-vessel disease.
2. Determine how many patients are potentially eligible for the randomised trial
3. How many are actually randomised and the reasons for non-randomisation.

4. Document mortality rates in the overall cohort of all PPCI patients in the registry in order that this can be compared with appropriate adjustment to those with multi-vessel disease (and the subgroup that are randomised).

All patients entered into the registry will be registered with the NHS Medical Research Information System (MRIS) for longer term passive follow-up for clinical outcomes in particular vital status. The intention is to also identify, if resources allow, hospital admissions through central NHS records (e.g. the HES database from the King's Fund).

### **Registry Inclusion criteria**

1. Suspected or proven acute myocardial infarction
2. Significant ST elevation on ECG
3. < 12 hrs of symptom onset
4. Scheduled for Primary PCI for clinical reasons
5. Provision of written informed consent

### **Registry exclusion criteria**

There are no formal exclusion criteria for the CVLPRIT registry for patients that meet the inclusion criteria.

## **12. RANDOMISED PILOT STUDY**

### **12.1 Inclusion Criteria**

1. Suspected or proven acute myocardial infarction
2. Significant ST elevation or left bundle branch block (LBBB) on ECG (In cases of LBBB, angiographic confirmation of IRA occlusion is required)
3. < 12 hrs of symptom onset
4. Scheduled for Primary PCI for clinical reasons
5. Provision of verbal assent followed by written informed consent
6. Multi-vessel coronary disease detected at time of angiography (see guidance below)

### **Guidance for classification of multi-vessel coronary disease**

- For this study MVD is considered to be the IRA plus at least one non-infarct related epicardial artery (N-IRA) with at least one lesion deemed angiographically "significant" (i.e. >70% diameter stenosis observed in at least one plane)
- The N-IRA should be a major (>2mm) epicardial coronary artery or branch (>2mm) and be suitable for stent implantation.

### **12.2 Exclusion Criteria**

1. Any contraindication to PPCI (presentation timing, inadequate arterial access etc)
2. < 18 years age
3. Contraindication to multi-vessel PPCI, according to operator judgement and the reasons will be documented
4. Previous Q wave myocardial infarction
5. Cardiogenic shock since consensus favours complete revascularization in shocked patients (30)
6. VSD or moderate/severe mitral regurgitation
7. Known severe chronic renal disease (i.e. stage 4 or 5), (serum creatinine>200µmol/l or eGFR<30ml/min)
8. Patients with previous Coronary Artery Bypass Graft (CABG).
9. Suspected or confirmed thrombosis of a previously stented artery
10. Only significant N-IRA lesion is a chronic total occlusion.

### **12.3 Recruitment**

The seven proposed CVLPRIT centres will recruit over 9-24 months. The PPCI centres involved have combined annual PPCI rates of about 2000 patients or about 160 per month.



Data suggests ~ 30% (600 patient over one year) will have significant non-infarct related artery disease and of these one half may be eligible and be randomised. This would result in 300 possible patients and the pragmatic total sample size for this study is 285.

#### **12.4 Angiographic Criteria for Presence of Significant Multi-Vessel Coronary Artery Disease**

Presence of multi-vessel coronary artery disease at angiography will be considered to be as at least one lesion in a non-infarct related artery (N-IRA) deemed angiographically significant (>70% luminal diameter narrowing in single, radiographic projection). The N-IRA should be a major epicardial coronary artery or major branch (>2mm) namely: Left anterior descending or large (>2mm) diagonal branch, Circumflex or large 1<sup>st</sup> or 2<sup>nd</sup> obtuse marginal branch, or a balanced/dominant right coronary artery including the posterior descending artery and left main stem. All lesions should be suitable for stent implantation (adapted from RITA-2 trial criteria; 31) The use of pressure wire interrogation to determine the functional significance of equivocal N-IRA lesions is permissible a guide to intervention. An uncorrected (Pd/Pa) fractional flow reserve of <0.80 may be taken as evidence of flow-limitation and an indication for PCI. It is understood that in acutely ill patients the decision to classify the coronary anatomy as fulfilling the study criteria for MVD or not has to be the decision of the primary operator.

#### **12.5 Randomisation**

Randomisation will occur following angiography but prior to PCI and will be performed centrally by an automated 24-hour telephone randomisation system. Back-up systems will be in place if there is any problem with the telephone randomisation method. An independent statistician will provide the randomisation tables. A centre investigator ID will be required to access the system which will be provided by the central co-coordinating centre. Randomisation will be performed by appropriately trained and approved staff at each centre. Once the patient is randomised they will be followed for the duration of the follow up irrespective of subsequent clinical management. The randomised groups will be:

##### **Group A : IN-PATIENT COMPLETE REVASCULARISATION**

- Immediate PPCI of IRA plus N-IRA (N-IRA can be treated at anytime during index hospitalisation at operators discretion but ideally within 36 hours of randomisation)

##### **Group B : CULPRIT LESION ONLY REVASCULARISATION**

- Immediate PPCI of IRA only as per routine clinical practice

### 13. TABLE 3: SUMMARY OF BASELINE, RANDOMISATION AND FOLLOW-UP PROCEDURES

	Pre-PPCI	PPCI	90 mins Post PPCI	12h post PPCI	<24 hours post PPCI	<36hours PPCI	Pre-discharge	6-8 weeks	6 months (telephone)	9-12 Months†
<b>REGISTRY PATIENTS</b>										
Assent										
Consent					X					
Demographics	X									
ECG	X									
Clinical status										X¶
<b>RCT PATIENTS</b>										
Assent	X									
Consent					X					
Demographics	X									
ECG	X		X					X		X
FBC	X			X						
U&E	X			X						
Troponin	X			X						
CK	X			X	X*					
ACT **		X								
NT-pro BNP							X			X
Complete revasc§						X				
CMRI							X‡			X‡
MPS								X		
Echocardiogram							X			X
EQ 5D							X			X
MRIS registration							X			
Document clinical status							X	X	X	X

¶: 9-12 month follow for registry patients can be performed by “passive” methods (medical records and/or MRIS) or if resources allow by telephone. No clinic visit is required

\*: CK is recommended to be collected on day 2 post-PPCI.

\*\*:: ACT (activated clotting time) should be assessed according to local lab standards, the values should be noted in the procedure protocol (source data)

§: in those randomized to complete revascularization. If not performed at time of initial PPCI, patient will require an additional procedure ideally <36 hours of randomisation

‡: CMRI (Cardiac Magnetic Resonance Imaging)

†: A final follow-up window is provided to allow flexibility for scheduling appointments and tests.

FBC = Full blood count

U&E = Urea, electrolytes, creatinine, e GFR

NT-pro BNP = N-terminal pro Brain natriuretic peptide

MPS = Myocardial Perfusion Scan

EQ-5D = EuroQol quality of life assessment

MRIS : Medical Research Information System

## 14. IN-HOSPITAL MANAGEMENT GUIDELINES

Further details of study related procedures including guidance for consent, clinical care and completing paper CRFs will be provided in the study Manual of Operations which will be issued to all sites and will form the basis of site training.

PCI procedures will be carried out according to current national and international guidelines and local practice. The use of Drug Eluting Stents (DES) are recommended in this study. However the decision will be left to the discretion of the treating interventional cardiologist ideally according to NICE guidance and other professional guidelines. and the type of stent will be recorded in the study database. Prior to PCI an ECG is recorded and blood drawn for FBC, U&Es, CK and Troponin T/I as per normal practice and results made available for trial purposes. All patients will have received oral clopidogrel or prasugrel loading dose as per local practice. The use of Abciximab/bivalirudin is recommended where appropriate and consistent with local institutional practice and this will be recorded. Specific procedural details will be recorded. In patients randomised to multivessel PCI, operators will be encouraged to undertake non-IRA PCI as early as possible (preferably during the initial PPCI procedure and if this is not possible, within 36 hours of randomisation), and in any case during the index hospital stay. The actual time post randomisation will be recorded. A meta-analysis and recent registry data suggest no safety issues and perhaps even efficacy benefit of DES (32,33). At 12 hours post PCI routine blood tests are repeated for CK, Troponin T/I, FBC and U&E as per usual clinical practice. Troponin T/I should be taken again if there any recurrent symptoms of ischaemia. Of note, patients found to have significant renal impairment after randomisation should be treated according to the best clinical practice. Prior to discharge a trans-thoracic echocardiogram undertaken for LV ejection fraction and regional wall motion abnormality. Cardiac magnetic resonance imaging scan will also be undertaken prior to discharge evaluating LV function, myocardium at risk and extent of fibrosis. Adverse events (efficacy and safety end-points) and secondary end-points are collected pre-discharge (Appendix 3). If there is an uncomplicated clinical course it is expected that patients will be discharged on day 3-4 (day of randomisation = day 0). Optimal secondary prevention therapy is mandated. A fuller explanation of the study will be provided 24 hours after initial procedure with a second stage consent for follow-up procedures.

All medication used should be deemed clinically appropriate for the individual patient by the local investigator. Loading with Clopidogrel/prasugrel or another licensed P2Y<sub>12</sub> inhibitor will be performed prior to PCI. Patients receiving bare-metal stents will receive up to 12 months of dual anti-platelet therapy according to NICE guidelines for ACS, as will those receiving DES. All patients will remain on aspirin (75-300 mg) for the continuation of the study period according to local practice. Other antiplatelet agents will be used according to their license, contemporary guidance and latest evidence from clinical trials. Patients who require additional anticoagulation can be treated additionally with an anticoagulant (Coumadin, warfarin) according to the clinical requirements. The CHADS<sub>2</sub> score should be calculated to decide the necessity of anticoagulation if the score is >2.

Patients should receive baseline secondary-prevention medication including a long-acting beta-blocker along (or rate-limiting calcium antagonist) with an ACE-inhibitor (or angiotensin II receptor antagonist [A2RA] if ACE-I intolerant) at maximum tolerated dose. Patients should receive a statin unless there is documented prior hypersensitivity. Lipid profile will be optimized as fully as possible. Patients with diabetes mellitus should be managed aggressively as per local guidelines with a period of insulin therapy to achieve good glycaemic control. Medications should be up-titrated to maximum tolerated dose within secondary-prevention recommendation to meet the treatment targets, with the use of additional anti-hypertensive medications permitted. Additional anti-anginal medications, e.g. non-dihydropyridine calcium antagonists or long-acting nitrates/ nicorandil are permitted but

their use is not considered a pre-requisite prior symptom-driven invasive investigation if adequate baseline secondary prevention medication has been established. Cardiac rehabilitation should be offered to all patients including dietary advice and referral for smoking cessation therapies. Within either group, continuous clinical monitoring should be maintained along with usual clinical care. Thus the onset of new symptoms consistent with ischaemia in haemodynamically stable patients should wherever possible be confirmed by non-invasive imaging test before considering coronary angiography. Suggested treatment targets for PPCI patients include:

- Random total cholesterol  $\leq 4\text{mmol/l}$ , LDL  $\leq 2\text{mmol/l}$
- BP  $\leq 130/80$  mmHg in all patients
- HbA1C  $\leq 7\%$  in diabetic patients

#### **14.1 Cardiac Magnetic Resonance**

Cardiac magnetic resonance scanning will be performed prior to discharge in patients who are willing and if facilities are available, according to the summary provided in Appendix 3.

#### **14.2 Procedures at discharge**

At discharge patients will have a NT pro-BNP, ECG and EQ-5D recorded, the study case report form will be completed and patients will be registered with MRIS.

### **15. FOLLOW-UP**

#### **15.1 Follow up at 6 weeks**

Patients will return for a myocardial perfusion scan at 6 weeks ( $\pm 2$  weeks) and documentation of clinical status. This scan will, in general, be “nested” (i.e. used for study purposes only) but made available to the operator if the ischaemic burden is deemed by the independent reporter to be  $>20\%$ . If this is the case, results of the scan will be forwarded to the clinician in charge of the patient who will then decide on clinical grounds to contact the patient with a view to intervention on the IRA or NIRA. All patients, other than those deemed by the clinician based on  $>20\%$  ischaemic burden to require early intervention, will undergo routine clinical follow up through their primary care physician. Patients will be informed to contact their general practitioner if they develop any problems during the course of the study. In general a second anti-anginal agent (e.g. long-acting nitrate/nicorandil) should be considered before non-invasive imaging with or without angiography. Patients with major or persistent symptoms will be referred back to the study team for review. In this study it is recommended that symptoms are investigated by non invasive imaging to confirm the likelihood that they are due to myocardial ischaemia, prior to consideration of PCI. PCI is allowed with ongoing CCS class III symptoms with a negative ischaemia test, if symptoms persist despite 2 anti-anginal medications at maximum tolerated doses, or if there is a further acute coronary syndrome. MPS will be undertaken in all patients as part of this study at 6-8 weeks as outlined above and results will be stored for analysis at a later stage (i.e. the results will be “nested”). If a patient develops symptoms within one month of this 6-8 week trial MPS then this test can be referred to (un-nested). If later than one month post routine trial MPS then a repeat scan should be undertaken. All MPS will be reviewed by a local expert in MPS for extent and location of reversible ischaemia. There is debate about the value of routine MPS after discharge and this study should determine whether this test should be routinely used 6-8 weeks after PPCI. Much of the information is transferable to other non-invasive modalities.

#### **15.2 Follow up at 6 months**

Patients will have a telephone follow-up to check for adverse events

### 15.3 Follow up at 9-12 months

The following tests and outcomes will be recorded at 9-12 months for **all patients in the randomised study**. Patients will need a clinic visit and ideally all information and procedures can be carried out on the same day.

- NT-pro BNP
- ECG
- Echocardiogram
- EQ-5D/ HE questionnaire
- Clinical status
- CMR

## 16. OUTCOME MEASURES

### 16.1 Primary clinical outcome

Composite of major adverse cardiovascular events (MACE) up to 12 months (time to first event):

- All-cause mortality
- Recurrent MI
- Heart failure
- Need for repeat revascularization

### 16.2 Secondary Outcome Measures

Individual components of primary composite outcome

1. Cardiovascular mortality
2. Main safety composite outcome at 12 months:
  - Emergency CABG,
  - Confirmed stroke
  - Major bleeding
  - Surgical repair of vascular complications
3. Proportion of patients presenting with PPCI with significant MVD
4. Ischaemic burden at 6-8 weeks (expressed as % of total ) by MPS
5. Economic assessment and cost efficacy at 12 months
6. Length of hospital stay
7. Contrast Induced Nephropathy (rise Cr >25%) or 44.2umol/l within 48hrs after angiography and persisting for at least 48 hours
8. Echocardiographic LVEF and wall motion score (Discharge and 12 Months)
9. Change in NT-ProBNP from pre-discharge to final follow up
10. Quality of Life Score at 12 Months (EuroQol questionnaire)
11. Infarct size, extent of microvascular obstruction, myocardium salvaged, LV volumes and EF at discharge and follow up by Cardiac Magnetic Resonance Imaging.

### 16.3 Definitions of study outcomes: see Appendix 1.

## 17. STATISTICAL ISSUES AND SAMPLE SIZE

This is a pilot study to evaluate the feasibility and safety of multivessel coronary revascularisation in the context of PPCI, and the results will be used to plan a larger study. As such it is inappropriate to perform a formal sample size estimation. We will however provide critical descriptive data and will be able to estimate recruitment rates, overall events rates in registry patients and sample sizes for future studies. For the registry (non-MVD and MVD not randomised) we expect about 1500 patients to be enrolled and thus we will have excellent data on patient characteristics, treatment patterns, clinical outcomes, accurate documentation of the proportion with significant multi-vessel disease, the proportion eligible

for CVLPRIT, the proportion actually randomised and the reasons why eligible patients were not randomised.

The event rate for death at 12 months is expected to be about 10% and death, MI, heart failure, and repeat revascularisation about 20%. Thus we will have about 240 events in the registry to perform descriptive and multivariate analyses on prognostic features, in particular the presence and severity of multi-vessel disease on the initial angiogram. Patient consent will be obtained for copying and storage of angiograms for subsequent analysis. Review of the Politi data (28) suggests that there may be a significant difference in outcome seen if 250 patients are randomised if absolute differences in outcome are as large as 12%. Analysis will be on an intention-to-treat basis. Quality of Life Scores will be determined from completion of a structured and validated EuroQoL questionnaire at pre-discharge and 9-12 month follow-up and will form part of the cost-benefit analysis. For the economic analysis the total cost of care will be determined in each group using agreed tariffs relevant to overall national costs incurred for treatment at the start of enrolment. Statistical assumptions for the CMR are provided in Appendix 3. Statistical support for the trial will be provided by an experienced statistician in CTEU and additional statistical expertise as required from the Imperial Clinical Trials Unit.

## **18. STUDY TIMETABLE**

The study is planned to start enrolment in 2011. Recruitment is planned to take place over about 24 months with a further 12 months for follow-up and close-out of the study. Thus *the study will run over 36 months. Study set up prior to enrolling the first patient including* obtaining ethical approval, signing Clinical Trial Agreements, training sites and preparing the electronic case report form will take about 6 months.

## **19. CONSENT**

Prior to PPCI patients will be requested to provide verbal assent to enter the randomised controlled trial (RCT). The assent process involves reading an ethically approved short narrative of the study to the patient and if the patient provides verbal agreement to enter the study (assent), this will be documented in the hospital record. Within 24 hours of the PPCI procedure, assuming the patient's clinical condition allows, full written informed consent will be obtained for the registry and/or RCT as appropriate. The assent process has been approved on ethical grounds for patients with critical conditions who are participating in clinical trials including the completed CRASH trial and the ongoing STREAM trial (34, 35). Thus patients will be required to provide written informed consent in order to participate fully in the study. Patient information sheets, consent forms and any amendments will be approved by National Research Ethics Service (NRES) prior to implementation. The process of consent requires individual discussion with the patient. Information should be provided in a language and at a level of complexity understandable to the subject in both oral and written form. Patients should not be coerced, persuaded, or unduly influenced to participate or remain in the trial. Patients should understand that they are free to withdraw from the trial at any point and that this decision will not affect the level of care they will receive. Before any trial-related procedures may be performed, assent must be obtained from the patient by the investigator or designated representative by means of a verbal declaration. Following the assent procedure, written informed consent must be obtained for the patient to be able to continue in the study (either registry or RCT). If patients provide verbal assent but not subsequent written consent, patients are not able to proceed in the study. Data already gathered may only be used if patients provide consent for this purpose, even if they do not consent to continuing in the study.

The original signed consent form should be stored at the centre in the trial site file, a copy in the patient's medical notes and a copy provided to the patient for their records. Consent is an ongoing process and investigators will be encouraged to discuss the study with patients after

the revascularisation procedure to ensure that they understand the study information and are happy to continue participating in the trial. Consent for this study may be obtained from the patient by qualified health professionals who have appropriate experience in this field and have been approved as a member of the study team by the local Principal Investigator. Typically consent is obtained by the local Principal Investigator, another Consultant, Specialist Registrar, Research Fellow or experienced nurse.

## **20. CONDUCT OF THE STUDY**

### **20.1 Research governance and regulatory framework**

This trial is a comparison of two strategies for coronary revascularization in acute MI in patients with significant multi vessel disease (“complete revascularisation” versus “infarct related artery only revascularisation”). This study does not require formal regulatory approval from the Medicines Healthcare Regulatory Authority. The trial will be conducted according to the principles of the Medical Research Council Good Clinical Practice guidelines, Declaration of Helsinki (<http://www.wma.net/>), Data Protection Act, NHS Research Governance and relevant local and national laws.

### **20.2 Ethics**

The study will be conducted in accordance with the Declaration of Helsinki (Revised 48<sup>th</sup> General Assembly, Somerset West, Republic of South Africa, October 1996). The Trial Protocol, patient information letters (PIL) and consent forms will be approved by the National Research Ethics Service (NRES) and each participating site will obtain Site Specific Approval from their NHS R&D department before commencing the trial. Any amendments to this protocol, the PIL and / or consent form will require approval from the Sponsor, Steering Committee and NRES prior to implementation. In addition, approval of amendments will be required by the local institution. A signed Clinical Trial Agreement is required before the study commences. A copy of the letter of approval from the NRES and each Research Office must have been received by the Coordinating Centre prior to any randomisation at that site. Records of local Institutional Review and Ethics Committee review and approval of all documents pertaining to this trial must be kept on file by the investigator in the Investigator File. Apart from the investigational procedures specified in the protocol, investigators may not perform ancillary studies without written approval from the Trial Steering Committee and appropriate ethical approval.

### **20.3 Data Handling and Record Keeping: Completion of Case Report Forms**

Case report forms (CRFs) will be maintained in paper form. The investigator and designated personnel must ensure accuracy, completeness and timeliness of data reported in the CRF and all required reports. Data reported on the CRF that are derived from source documents should be consistent with the source documents or the discrepancies should be explained. Within one week after completion of each visit, Data will be recorded onto two part No Carbon Required (NCR) paper CRFs and the top copy sent to the CTEU at the times specified.

### **20.4 Confidentiality**

The aim and contents of the study, in addition to its results are to be treated as confidential by all persons involved in the clinical trial.

### **20.5 Responsibilities**

Handling of data, storage of data, planning, assessment and quality assurance are regulated by the recommendations on Good Clinical Practice of the International Conference on Harmonisation (ICH) and these regulations apply to the study and all study related personnel including Investigators, Monitors and agents of the Sponsor.

## **20.6 Archiving**

On termination of the trial, the source documents are to be archived until at least 5 years after the last reporting of data in an official manuscript.

## **21. ASSESSMENT OF SAFETY**

### **21.1 Adverse events**

Information about trial outcomes and adverse events will be collected from randomisation until the end of the trial.

### **21.2 Definitions of Adverse Events**

#### **Adverse Event (AE)**

Defined as any untoward medical occurrence.

#### **Serious Adverse Events (SAE)**

A Serious Adverse Event (SAE) is defined as any untoward medical occurrence that:

- results in death
- is life-threatening

NB: The term "life-threatening" in the definition of "serious adverse event" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

- requires hospitalisation or prolongation of existing inpatient's hospitalisation
- results in persistent or significant disability or incapacity
- results in a congenital anomaly or birth defect

### **21.3 Expected serious adverse events/clinical outcomes**

Some serious adverse events occurring in this trial will be expected as a consequence of the underlying disease, routine treatments or diagnostic tests or study related investigational procedures. In addition, prespecified clinical outcome measures in the study will not be considered SAEs. The CRF will be designed to capture expected clinical outcomes.

### **21.4 Expected serious adverse events**

- Death
- Myocardial infarction
- Recurrent ischemia
- Stroke
- Heart failure
- Cardiogenic shock
- Cardiac rupture or tamponade
- Ventricular septal defect
- Valve regurgitation
- Vascular trauma related to PCI
- Arterial or venous embolic events
- Minor and major bleeding
- Revascularisation procedure (PCI or CABG)
- Hospital admission for a cardiovascular cause
- Renal impairment due to pre-existing renal disease and/ or contrast load during angiogram
- Haematoma at angiogram/PCI access site



- Arrhythmias (supraventricular or ventricular)
- Admission or procedure for a pre-existing condition

### **21.5 Classifying SAEs**

All SAEs will be assessed for causality and expectedness.

- Related events are those that are considered to have resulted from the administration of any research procedures. These include PCI, CMR, and myocardial perfusion scanning.
- Unexpected events are those that are not listed in this protocol or the participating centres clinical patient information sheets for procedures.

### **21.6 SAE reporting**

Centres will be required to report all SAEs to the Coordinating Centre within 24 hours of identification of the event. Investigators will be required to identify if the event is related or expected. Upon receipt, SAEs will be reviewed by the Chief Investigator or a designated colleague to assess expectedness and causality. All the events are then reviewed by independent medical expert for causality and expectedness. SAEs that are related and unexpected will be reported to the Research Ethics Committee within 15 days of receipt by the Coordinating Centre. A summary of safety will be included in the annual progress report to the Ethics committee.

### **21.7 Institutional Approval**

A study can only start at a participating centre when the following conditions have been met:

1. Ethical approval has been obtained
2. A Clinical Trial Agreement (CTA) has been signed by the site and Sponsor
3. A list of all study related personnel has been obtained including their short CVs, study responsibilities and signatures
4. A site set up visit has been carried out to ensure sites have provided adequate resources including personnel, space and time to carry out the study effectively
5. All study related personnel have been trained in the study related procedures, the protocol, data collection, Good Clinical Practice and obtaining informed consent if they are expected to do this.
6. The Research Office at the participating site has issued a letter of authorisation declaring that the study may start at that centre and a copy of this letter is provided to the Coordinating Centre
7. The centre has been given authorisation to start the study by the Coordinating Centre.

## **22. STUDY ORGANISATION AND COMMITTEES**

### **22.1 Sponsor**

The Sponsor's role is clearly set out in the NHS Research Governance documents. The Sponsor is the University Hospitals of Leicester NHS Trust. Research agreements will be held with the participating sites and collaborating groups. The Clinical Trials and Evaluation Unit (CTEU) of the Royal Brompton & Harefield NHS Foundation Trust will be responsible for ensuring the study is conducted to the standards set out in the NHS Research Governance Framework and it is expected that the Sponsor will delegate many of the day to day Research Governance responsibilities to CTEU including trial management, data management, adverse event reporting and site monitoring.

## **22.2 Funding Sources**

The study has been funded by grants from the British Heart Foundation (Grant award number SP/10/001/28194) and Efficacy and Mechanism Evaluation Programme from Medical Research Council and National Institute for Health Research (Grant award number 10-27-01). Additional support and resources for the trial will be provided by the participating Trusts and their corresponding Comprehensive Local Research Networks (CLRN).

## **22.3 Trial Steering Committee (TSC)**

A Trial Steering Committee consisting of the Principal Investigators, a representative of CTEU and a representative of the Sponsor will be convened. The TSC will be responsible for the scientific and ethical conduct of the study and will supervise progress of the trial. There will be an independent Chair of the TSC (i.e. an individual with experience in clinical research who is not part of the trial team). The trial protocol and subsequent amendments will be approved by the TSC. The TSC members will be required to attend TSC meetings which will be held prior to the start of the trial and as required throughout the trial. A subgroup of the TSC, the Trial Management Group (TMG) consisting of the Chief Investigator representatives of CTEU and additional members as appropriate, will meet weekly by telephone to ensure that the study runs smoothly and according to the pre-agreed timetable.

## **22.4 Data Monitoring Committee (DMC)**

An independent Data Monitoring Committee will be convened and meet at least annually to provide independent advice on study conduct and safety issues. Meetings will also be held as necessary should any urgent issues occur. The DMC will develop a charter which describes the framework within which it will operate.

## **22.5 Clinical Events Review**

An independent medical expert reviews the details of trial outcomes and SAEs. His/her reports will be used in the assessment of endpoints.

## **22.6 Trial Management Centre**

Trial Management will be conducted by the Clinical Trials and Evaluation Unit (CTEU) of the Royal Brompton and Harefield NHS Foundation Trust in collaboration with the Chief Investigator and representatives of the sponsor. CTEU is a dedicated cardiovascular and respiratory trials unit that is part of the registered Imperial Clinical Trials Unit, and has experience in the field of coronary revascularisation trials. CTEU will be responsible for day to day management of the trial including the following: development of the protocol, ethical submissions, development of the specification for the data collection system, data management, meeting arrangements, quality assurance and preparation of trial documentation. CTEU will ensure that the trial runs according to the pre-agreed timetable, ethical requirements are complied with, and that all aspects of the study are performed to the highest quality. The CTEU will also assist in the training of investigators and co-ordinators at the start-up of the study.

## **22.7 Local Principal Investigator Responsibilities**

Investigators must ensure that all relevant local approvals have been obtained as well as agreements signed off by their Institution prior to the start of the study. Investigators are responsible for performing the study in accordance with the principles of MRC Good Clinical Practice guidelines, the Declaration of Helsinki (<http://www.wma.net/>), NHS Research Governance and all local laws. Investigators are required to ensure compliance to the protocol, data collection system and Manual of Operations. Investigators and their Institutions are required to allow access to study documentation or source data on request for monitoring visits and audits performed by the CTEU, representatives of the Sponsor or any regulatory authorities.

## **22.8 Centre visits**

### **22.8.1 Initiation visit**

Before the study commences each centre will receive a training visit from staff at the CTEU. These visits will ensure that personnel at each site (including principal investigators, co-investigators and the study site co-ordinator) fully understand the protocol, data collection system and the practical procedures for the study and that sufficient resources to carry out the study are available at each centre.

### **22.8.2 Interim monitoring visit**

During the study, CTEU will perform monitoring visits to each centre. The purpose of these visits is to ensure compliance to the protocol and that ethical requirements are met. Source data verification and checking of essential documents will be performed. Monitoring visits also provide an opportunity for further training if required (e.g. new staff). Central review of study data will also be performed throughout the study by the data management team at CTEU.

### **22.8.3 Close out visit**

At the end of the study each centre will receive a site visit to resolve any outstanding edit queries or adverse events and to verify the archiving arrangements for study documentation.

## **22.9 Insurance and Indemnity**

If the patient is harmed by taking part in this research project there are no specific indemnity and /or compensation arrangements. If a patient is harmed due to negligence, then the patient may have grounds for legal action, but they may have to pay for this. Regardless of this, if they wish to complain about any aspects of the way they have been treated or approached during the research project, the standard National Health Service complaint system will be available to them.

## **22.10 Data Records and Archiving**

The Investigator must maintain the confidentiality of all study documentation, and take measures to prevent accidental or premature destruction of these documents. It is recommended that the Investigator retain the study documents for at least 5 years after the results from the Pilot Study has been reported. In the event that a longer period is required the Investigator or Sponsor must notify the relevant parties. The Investigator is responsible for ensuring that archiving can be maintained for five years locally, if this situation changes and archiving can no longer be ensured, the Investigator shall inform the Sponsor and the relevant records shall be transferred to a mutually agreed upon designee.

## **22.11 Audits and inspections**

For the purpose of ensuring compliance with the Clinical Trial Protocol, Good Clinical Practice and applicable local requirements, the Investigator should permit auditing by or on the behalf of the Sponsor. The Investigator agrees to allow the auditors/inspectors to have direct access to his/her study records for review, and should understand that these personnel are bound by professional confidentiality, and as such will not disclose any personal identity or personal medical information. The Investigator will make every effort to help with the performances of the audits and inspections, giving access to all necessary facilities, data and documents. The confidentiality of the data verified and the protection of the patients should be respected during these inspections. The Sponsor or its representative will immediately communicate any results and information arising from the inspections. The Investigator shall take appropriate measures as required by the Sponsor to take correctives actions for all problems found during the audit or inspections.

## **22.12 Data protection**

The patient's personal data and Investigator's personal data, which may be included in study related databases, shall be treated in confidence and in compliance with all applicable laws and regulations. When archiving or processing personal data, the Sponsor or its representative shall take all appropriate measures to safeguard and prevent access to this data by any unauthorised third party. All data obtained in the context of the clinical trial are subject to data protection. The patient's name in addition to other data related to persons (excluding date of birth, age and sex) are not to be disclosed by the Investigator or the investigating physicians. The latter shall take care that the case report forms or other documents (e.g., copies of reports on special findings) transmitted to the review committees or the coordinating centre contain no names, but only either initials or date of birth and study number. The storage of data for electronic statistical assessment shall be performed only under the patient's study number. Only the local site Principal Investigator can perform assignment of the study identifier to the personal data for patients at their own site. If it becomes necessary in the course of the study to identify a patient's name for medical reasons, all the individuals involved are subject to an obligation to maintain secrecy. If personal data are stored and processed, for example to link a patient to MRIS records, the requirements of data protection legislation are to be observed and specific patient consent required for this.

## **22.13 Trial registration**

The CVLPRIT trial will be registered on a recognised clinical trials database prior to recruitment commencing.

## **22.14 End of trial**

The trial will end when all patients have completed the observation period (i.e. when the last patient recruited has completed the 12 month follow-up assessment). Longer term "passive" follow up will continue through MRIS. Consent for this will be obtained from patients for a period of up to 20 years.

## **22.15 Expertise of personnel and centres taking part**

The study proposes to register all patients presenting for PPCI and follow them for up to 12 months, and to randomise those with multi-vessel disease to complete early revascularisation or not. All centres and the principal investigators have extensive experience of primary angioplasty and managing patients with acute myocardial ischaemia. The Chief Investigator has had a long track record in clinical research in PCI including the important REACT trial published in the New England Journal of Medicine (36). The study will be coordinated by the Clinical Trials and Evaluation Unit (CTEU) of Royal Brompton and Harefield NHS Foundation Trust, an academic research group with 14 years of expertise of clinical trial management including study monitoring and data management. CTEU is now part of the nationally registered Imperial Clinical Trials Unit (ICTU). CTEU has an extensive track record in the successful management of coronary revascularisation trials including Stent or Surgery (998 patients in 42 centres), Arterial Revascularisation Trial (ART: 3100 patients from 28 centres) CARDia (510 patients from 18 sites), and CARESS (600 patients from 23 European centres) (37-40). All of these trials have been academically led, and ART is funded jointly by a grant from the MRC and British Heart Foundation.

## **22.16 Publication Policy**

The Chief Investigator will be responsible for ensuring that the results of the study are submitted for publication in a peer review journal irrespective of the outcome within 6 months after the database is locked. Authorship on the manuscript will be determined by the Chief Investigator according to contribution to the study after discussion with the Trial Steering Committee and according to the guidelines of leading medical journals. A full list of

investigators shall be included in the original publication as an appendix. The TSC will be responsible for approval of all manuscripts arising from the study prior to submission for publication. All publications will quote the ISRCTN number and will acknowledge the participating investigators, TSC and DMC, CTEU the Sponsor and the Funder

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## **APPENDIX 1: Definitions of clinical events**

### **1. Death**

Death from any cause classified as cardiovascular or non cardiovascular. Cardiovascular death includes any cardiac causes, or other vascular causes (e.g. pulmonary embolism, aortic dissection).

### **2. Myocardial infarction (MI):**

Myocardial infarction will require a hospital admission with one or more of the following:

**Type 1:** Spontaneous re-MI: Recurrent angina symptoms or new ECG changes occurring before PCI or <48 hours from PCI that is compatible with re-MI associated with an elevation of CK-MB, troponin, or total CK beyond ULN and 20% or more above the previous value.

**Type 4a:** CK-MB or total CK >3 times the ULN within 48 hours following PCI. If the pre-PCI CK-MB or total CK level is higher than the ULN, there also needs to be:

- either the demonstration of a falling CK-MB or total CK level prior to the onset of the suspected event,
- or a subsequent peak of the cardiac biomarker of at least 20% above the previous value obtained prior to the onset of the suspected event.
- With either an appropriate clinical presentation or new ischemic ECG changes (ST-segment depression or ST-segment elevation or development of new pathological Q waves/LBBB).

Type 4b: Myocardial infarction associated with stent thrombosis as documented by angiography or at autopsy AND fulfilling the criteria of spontaneous MI (Type 1)

### **3. Heart failure**

Heart failure will be defined as a hospital admission with any of the following symptoms and signs: worsening breathlessness, fatigue, fluid overload, pulmonary oedema, elevated venous pressure and elevated BNP. Confirmation of heart failure according to local expert judgement and evidence of impaired LV function will be required for the event to be classified as heart failure.

### **4. Repeat Revascularisation**

Repeat revascularizations classified as:

1. target lesion re-interventions (TLR) inside the implanted stent or within 5 mm proximally or distally or repeated interventions in the same vessel (TVR) by percutaneous coronary interventions (PCI) or by coronary artery bypass graft surgery.
2. PCI to lesions not identified previously
3. CABG for new symptoms or complications of PCI

### **5. Stent thrombosis**

Stent thrombosis (ST) will be classified as “acute”- within 24 hours from the procedure, “sub-acute” up to 30 days, “late” from 30 days till 1 year and “very late” after 1 year after index procedure. Thrombosis will be classified as definite, probable and possible according to the definition of Academic Research Consortium[25]. ST will be defined as the occurrence of one of the following events:

1. Angiographic documentation of complete or partial stent occlusion and target vessel related acute clinical ischemic event.
2. Autopsy documentation of complete or partial thrombotic stent occlusion
3. Myocardial infarction in the distribution of the stented vessel.

We will separately evaluate the incidence of possible ST by including all unexplained death after 30 days.

## **6. Emergency CABG**

This will be defined as CABG occurring within 48 hours of an ischaemic event in a patient who was not previously scheduled to have CABG.

## **7. Stroke**

Defined as the presence of a new focal neurologic deficit thought to be vascular in origin, with signs or symptoms lasting more than 24 hours. It is strongly recommended (but not required) that an imaging procedure such as CT scan or MRI be performed. Stroke will be further classified as ischaemic, haemorrhagic or type uncertain.

## **8. Major bleeding**

Major bleeding defined as the cumulative occurrence of intracranial or intraocular bleeding, haemorrhage at the vascular access site requiring intervention, a reduction in haemoglobin levels of at least 5 grams per deciliter, reoperation for bleeding or transfusion of a blood product (at least 2 units), bleeding causing substantial hypotension requiring the use of inotropic agents. All other bleeding events were considered as minor (i.e. epistaxis, blood traces in the stool etc.)

## **9. Surgical repair of a vascular complication**

In general this will refer to surgical repair to the femoral or radial arteries following PPCI but could refer to venous complications or in unusual circumstances repairs to the aorta or carotid arteries.

## APPENDIX 2: Draft list of core data to be collected

Baseline demographic data, co-morbidities
Onset of pain
Infarct territory
Time of call for help
Time of first medical contact
Time of arrival at PCI centre (door)
Vascular access site used (Femoral/ radial)
Time of balloon inflation
Maximal ST-segment elevation, which lead
Post-procedure ST-segment elevation (same lead)
Time at which maximal ST-segment elevation first falls to 50% of maximum
Lesion(s) site Grade (s) A, B1,B2, C
Time of 1 <sup>st</sup> Balloon Inflation (Pain onset recorded in CRF)
Number of significant lesions
Number of lesions attempted
Number of lesions successfully treated*
Pre-dilatation Y/N (each lesion)
Number of stents implanted
Pre TIMI flow (IRA)
Post TIMI flow (IRA)
ACT therapeutic Y/N
Clopidogrel 600mg pre-loading given
Reopro: Bolus Y/N; Infusion Y/N Why not used:
Visible thrombus present: No visible thrombus/ +/- ++
Thrombectomy device used? – Name of device
Contrast load
Screening time
IABP use
Peri-procedural complications
Procedure time
Number of vessels treated at index PPCI
Timing of subsequent N-IRA lesion PCI
Is this a STEMI eligible for P-PCI
Does the patient have multi-vessel disease
Is the patient being randomised
Reason for non-randomisation following angiography

Alternative diagnosis (not STEMI) suspected
Clinical deterioration- cardiovascular
Clinical deterioration- other
Diffuse non-IRA disease
Poor tolerance of angiography procedure
Operator decision not suitable for MV PCI- lesion characteristics (e.g. tortuosity, calcium)
Operator decision not suitable for MV PCI- patient characteristics (e.g. general frailty)
Operator decision not suitable for MV PCI-patient and Lesion characteristics
Patient failure to consent
Patient withdrawal of consent
Operator fatigue
Peri-procedural complication
Other (please comment)
Where initially randomised but withdrawn from study following randomisation
Clinical deterioration- cardiovascular
Clinical deterioration- other
Pharmacological (e.g. allergy)
Diffuse non-IRA disease
Poor tolerance of PPCI procedure
Operator fatigue
Peri-procedural complication
Revised operator discretion regarding suitability for IP MV PCI
Patient withdrawal of consent
Other (please comment)

### **APPENDIX 3. Cardiac Magnetic Resonance (CMR) Summary**

There are no published data on infarct size or myocardial salvage on CMR comparing the different treatment strategies. CVLPRIT-CMR is the first study that will systematically assess and quantify additional non-culprit artery related infarction and its prognostic significance in patients with multivessel disease at the time of PPCI. This 'additional infarction' cannot be quantified by traditional biomarkers as the increase in cardiac enzymes seen in STEMI patients masks any smaller increases that may be related to non-culprit lesion PCI.

Additional research costs for study related CMR scans (up to 2 per patient) have been provided through a grant awarded by the MRC/ NIHR Efficacy and Mechanistic Evaluation Programme. CMR will be carried out in patients randomised into the CVLPRIT pilot study if ethical approval is obtained. It is likely not all patients will be eligible due to contraindications to CMR or unwillingness to the CMR. Co Principal Investigators specialising in CMR will be appointed at each participating site and protocols and standard operating procedures prepared for the investigational procedures.

The CMR protocol will be standardised in all four centres on 1.5T platforms. All CMR scans will be analysed in the core laboratory based at Glenfield Hospital and will be blinded to patient treatment allocation. Dr G McCann is the Lead Investigator for the CMR and will be directly responsible for the supervision of a dedicated research fellow who will perform the analyses using specialised CMR post-processing software (Mass©, Medis, Leiden, NL). Functional assessment of LV ejection fraction, volumes and mass will be assessed according to current standards with the use of steady state, free precession sequence of the whole LV with 8-12 contiguous short axis slices. Rest perfusion will be performed after functional imaging and T2w (STIR) imaging and late enhancement images acquired using an inversion recovery prepared T1 weighted gradient-echo sequence in identical short axis slices commencing 10 minutes after the first contrast (gadolinium 0.2mmol/kg) injection in all patients.

Quantification of LV volumes, mass, oedema and scar characteristics will be performed on both short axis data sets in a random, blinded fashion. LV mass and volumes will be corrected for body surface area, and scar size assessed manually by delineation of the hyperenhanced area on each short axis slice, adding all slices to generate infarcted mass. Hypo-enhanced areas within the infarcted zone will be quantified separately to indicate the extent of MVO and will be included in total scar volume. The area at risk will be quantified by adding all areas of signal intensity on T2w greater than 2 standard deviations higher than remote myocardium. Salvaged myocardium will be calculated as the difference between hyperenhanced T2w mass and necrotic myocardium on delayed contrast imaging. Patients will be imaged between 48 and 72 hours after AMI to limit variation in MVO, which is a dynamic process(54). Salvaged myocardium will be expressed as a percentage of area at risk and total LV size and MVO will be quantified in grams, expressed as a percentage of infarct size, area at risk and LV mass.

New myocardial injury at follow-up will be determined by comparing paired CMR scans and will be agreed with 2 observers (GPM/fellow). Intra-observer and inter-observer variability will be calculated for 10 pre-discharge and 10 follow-up scans. For acute and chronic infarct size reproducibility, inter and intra-observer variability have been reported to be <1%. Stress CMR was considered for ischaemic burden pre-discharge but it was felt that this would be underestimated in the complete revascularization group due to impairment of endothelial function(41) post PCI. At follow-up ischaemic burden will be assessed on first pass perfusion semi-quantitatively by the summed difference score(42) after 3 minutes infusion of adenosine at 140mcg/kg/min. Antianginal medications will NOT be discontinued for the stress scan.

### **Sample size and proposed statistical analysis**

The power calculation is based on an infarct size of 20% with a standard deviation of 10% for culprit-only revascularisation which is consistent with previously published literature and with our own experiences in STEMI. The CMR scans will have 81% power to detect a 4% absolute difference in CMR measured infarct size between the different strategies being tested assuming 100 patients in each arm complete CMR. Importantly, this level of revascularisation related infarct has been shown to be independently associated with a 3 fold increase in Major Adverse Cardiovascular Events (MACE) in 152 patients followed up for a median of 2.9 years and is therefore clinically significant.

**Effect size:** There are robust data demonstrating that 30% of patients having elective PCI experience significant new myocardial infarction, the extent of which is 5% of total LV mass or 1.4% of LV mass for the entire group(3). This is despite at least 24 hours preloading with Aspirin and Clopidogrel and use of a potent glycoprotein IIb/IIIa platelet inhibitor (Abciximab) at the time of PCI in all patients. The risk of periprocedural MI is increased to 53% in patients with unstable angina undergoing PCI(4) and if repeated in CVLPRIT would increase infarct size for the complete revascularisation group by 2.6% of LV mass. We believe that the frequency of additional infarction in patients experiencing STEMI will be increased further. Preloading of anti-platelet agents occurs only within 1-2 hours before the P-PCI, and therefore microembolisation is likely to be increased compared to elective/semi-elective patients undergoing PCI. Patients with severe triple vessel disease will also have PCI to more than 1 non-culprit infarct related artery increasing the amount of additional injury. There is also an acute reduction in endothelial function/perfusion following PCI, that is likely to reduce flow to the peri-infarct zone, thereby increasing infarct size further. For the above reasons we believe that an effect size of increasing the total infarction by 4% of LV mass is justified and would be clinically important. Another study comparing different revascularisation strategies at the time of P-PCI has shown positive results using a similar power calculation for CMR measured infarct size, which is a further indication that our effect size is justified. Given the importance of the AAR at risk in the final determination of infarct size, myocardial salvage index will also be assessed. Assuming 90 patients in each arm (allowing for 10% scans excluded for technical reasons) we will be able to detect a difference in myocardial salvage index of 0.1, with 80% power assuming mean culprit-only index of 0.46 with a common standard deviation of  $\pm 0.24$ (37), and 2-tailed  $\alpha=0.05$

The aim of the statistical analysis is to detect clinically significant differences which may arise from the two revascularisation strategies being tested. The stratified randomisation procedure should help ensure that the groups are well matched at baseline. The primary analysis will be by intention to treat but a secondary analysis will also be performed by treatment received. Groups will be compared by 2 sample t- tests, Fisher's exact test and chi square analysis as appropriate. The complete revascularisation group will be split in to those with complete at the time of P-PCI and those with staged intervention. Univariate and multivariate predictors of MACE will be assessed by logistic regression analysis for the study cohort as a whole and by treatment strategy. There is a planned interim analysis after the first 120 patients have been recruited and the results will be given to the independent DSMB. Event free survival will be assessed by Kaplan-Meier analysis.