Appendix C

Review Protocol – Patient information	
Component	**Description**
Review question	**What are information needs of patients with stable angina regarding their condition and its management?**
Population	Adults with a diagnosis of stable angina • including people with diabetes, South Asians, women, minimal coronary heart disease
Intervention	
Comparison	
Outcomes	**Information on -** • **Condition and the symptoms** • **Treatment** Side effects of Drugs Choice of drugs Choice of treatment (drugs or revascularization) • **Post treatment care** Need for Rehab Type of rehab Diet • **Prevention** • **Activities for daily living** • **Quality of life** • **Prognosis /complications-** **As reported in the papers**
Search strategy	The databases to be searched are, Medline, Embase, The Cochrane Library, CINAHL, Psych info

Search terms	Patient/client Perception/view/opinion/experience/satisfaction/attitude /perspective/preference/ feedback/expectation/ beliefs/cooperation/ buy-in/ participation/involvement Patient centered/focussed care
The review strategy	Qualitative studies Questionnaires/ interviews/ focus groups groups/surveys Year restriction

Review Protocol – Treatment and Prevention of episodes of angina

Component	**Description**
Review question	**What is the clinical /cost effectiveness of short acting drugs for the management of anginal symptoms?**
Population	• Adults with a diagnosis of stable angina including people with diabetes, South Asians, women, refractory angina (prophylaxis), minimal coronary heart disease • Patients who have recurrence of anginal symptoms following revascularisation.
Intervention	Short acting nitrate by buccal, lingual or sublingual administration Glyceryl trinitrate – tablet, spray • Nifedipine capsule by sublingual/buccal administration
Comparison	• Nitrate spray vs. nitrate tablet • Nifedipine vs placebo • Nifedipine vs nitrate spray • Nifedipine vs nitrate tablet
Outcomes	<u>Immediate improvement</u> in exercise tolerance – within 30 mins of intervention *Preferred outcome:* • Change in total exercise time *Other outcomes:* • Change in time to ST depression • Change in time to onset of symptoms • Change in time to stopping exercise • Change in workload <u>Frequency and/or severity of angina</u> (and prophylaxic use) *Preferred outcomes:* • Time to relief of pain • Incidence of angina post- intervention *Other outcomes:* • Pain severity • Duration of pain

	Important adverse events (headache and syncope)
Search strategy	The databases to be searched are Medline, Embase, The Cochrane Library, CINAHL Randomised controlled trials (RCTs) will be considered. If no RCTs are found for certain outcomes such as adverse events, well conducted cohort studies and observational studies may also be considered. Studies will be restricted to English language only No date restriction will be applied. Databases will be searched from their date of origin
The review strategy	*Preferred:* • Double blind RCTs • Minimum number of participants n=50 (consider studies with smaller sample size if large numbers are not available) • >60% stable angina • Adverse event data to be sourced from RCTs only

Review Protocol – BB vs CCB	
Component	**Description**
Review question	**What is the comparative clinical /cost effectiveness of standard antianginal drugs (calcium channel blockers, long acting nitrates) for the management of angina?**
Population	• Adults with a diagnosis of stable angina • including people with diabetes, South Asians, women, minimal coronary heart disease
Intervention	Beta blockers atenolol , propranolol, bisoprolol, metoprolol, nadolol, Calcium channel blockers amlodipine, diltiazem, felodipine, nifedipine, verapamil)
Comparison	BB vs CCBs
Outcomes	Mortality @ longest available evaluation time point (preferred 5yr, 10 yr) Preferred outcomes: All cause mortality • Cardiac mortality Other outcomes: • Cardiovascular mortality

	Angina frequency/severity *Preferred outcomes:* • Angina incidence reported in diaries • GTN usage • CCS score Exercise tolerance (based on repeat of baseline ETT at a min of 3months follow up) *Preferred outcomes:* • Total exercise time Major cardiac events @ longest available evaluation time point (preferred 1yr, 5yr, 10yr) *Preferred outcome:* • Nonfatal MI Hospitalisation @ 6m -1yr Revascularisation @ 1yr, 5yr, 10yr if available Quality of Life eg EQ-5D, SF-36, HAD, etc @ longest available evaluation time point (preferred 1y, 5y, 10y)
Search strategy	The databases to be searched are Medline, Embase, The Cochrane Library, CINAHL and AMED. Randomised controlled trials (RCTs) will be considered. If no RCTs are found for certain outcomes such as adverse events, well conducted cohort studies and observational studies may also be considered. Studies will be restricted to English language only No date restriction will be applied. Databases will be searched from their date of origin
The review strategy	*Preferred:* • Double blind RCTs • Minimum n=50 or N=25 if cross over trial • >60% stable angina • Minimum Follow Up = 3m • Adverse event data to be sourced from RCTs only For longer term outcomes (> 1 year) • Double blind RCTs • Minimum N=200 (consider studies with smaller sample size if large numbers are not available) • >60% stable angina • Adverse event data to be sourced from RCTs only

Review Protocol – BB + CCB	
Component	**Description**
Review question	**What is the comparative clinical /cost effectiveness of standard antianginal drugs (calcium channel blockers, long acting nitrates) for the management of angina?**
Population	• Adults with a diagnosis of stable angina • including people with diabetes, South Asians, women, minimal coronary heart disease
Intervention	Beta blockers atenolol , propranolol, bisoprolol, metoprolol, nadolol, Calcium channel blockers amlodipine, diltiazem, felodipine, nifedipine, verapamil
Comparison	B blocker vs. B blocker+ CCB CCB vs. B blocker+ CCB
Outcomes	Mortality @ longest available evaluation time point (preferred 5yr, 10 yr) Preferred outcomes: • All cause mortality • Cardiac mortality Other outcomes: • Cardiovascular mortality Angina frequency/severity *Preferred outcomes:* • Angina incidence reported in diaries • GTN usage • CCS score Exercise tolerance (based on repeat of baseline ETT at a min of 3m follow up) *Preferred outcomes:* • Total exercise time Major cardiac events @ longest available evaluation time point (preferred 1yr, 5yr, 10yr) *Preferred outcome:* • Nonfatal MI Hospitalisation @ 6m -1yr

	Revascularisation @ 1yr, 5yr, 10yr if available Quality of Life e.g. EQ-5D, SF-36, HAD, etc @ longest available evaluation time point (preferred 1y, 5y, 10y)
Search strategy	The databases to be searched are Medline, Embase, The Cochrane Library, CINAHL and AMED. Randomised controlled trials (RCTs) will be considered. If no RCTs are found for certain outcomes such as adverse events, well conducted cohort studies and observational studies may also be considered. Studies will be restricted to English language only No date restriction will be applied. Databases will be searched from their date of origin
The review strategy	*Preferred:* • Double blind RCTs • Minimum n=50 or N=25 if cross over trial • >60% stable angina • Minimum Follow Up = 3m • Adverse event data to be sourced from RCTs only For longer term outcomes • Double blind RCTs • Minimum N=200 (consider studies with smaller sample size if large numbers are not available) • >60% stable angina • Adverse event data to be sourced from RCTs only

Review Protocol – Addition of long-acting nitrates	
Component	**Description**
Review question	**What is the comparative clinical /cost effectiveness of standard antianginal drugs (calcium channel blockers, long acting nitrates) for the management of angina?**
Population	• Adults with a diagnosis of stable angina • including people with diabetes, South Asians, women, minimal coronary heart disease
Intervention	Beta blockers atenolol , propranolol, bisoprolol, metoprolol, nadolol, Calcium channel blockers amlodipine, diltiazem, felodipine, nifedipine, verapamil)

	Long acting nitrates Isosorbide dinitrate Isosorbide mononitrate
Comparison	B Blocker + CCB vs. B Blocker + nitrates B Blocker + CCB vs. B Blocker + CCB + nitrates B Blocker vs. B Blocker + nitrates CCB vs. CCB + nitrates B Blocker vs. CCB + nitrates CCB + B Blocker vs. CCB + nitrates
Outcomes	Mortality @ longest available evaluation time point (preferred 5yr, 10 yr) Preferred outcomes: All cause mortality • Cardiac mortality Other outcomes: • Cardiovascular mortality Angina frequency/severity *Preferred outcomes:* • Angina incidence reported in diaries • GTN usage • CCS score Exercise tolerance *Preferred outcomes:* • Total exercise time Major cardiac events @ longest available evaluation timepoint (preferred 1yr, 5yr, 10yr) *Preferred outcome:* • Nonfatal MI Hospitalisation @ 6month -1yr Revascularisation @ 1yr, 5yr, 10yr if available Quality of Life eg EQ-5D, SF-36, HAD, etc @ longest available evaluation timepoint (preferred 1y, 5y, 10y)

Search strategy	The databases to be searched are Medline, Embase, The Cochrane Library, CINAHL and AMED. Randomised controlled trials (RCTs) will be considered. If no RCTs are found for certain outcomes such as adverse events, well conducted cohort studies and observational studies may also be considered. Studies will be restricted to English language only No date restriction will be applied. Databases will be searched from their date of origin
The review strategy	*Preferred:* • Double blind RCTs • Minimum n=50 or N=25 if cross over trial • >60% stable angina • Minimum Follow Up = 3m • Adverse event data to be sourced from RCTs only For longer term outcomes • Double blind RCTs • Minimum N=200 (consider studies with smaller sample size if large numbers are not available) • >60% stable angina • Adverse event data to be sourced from RCTs only

Review Protocol - Nicorandil	
Component	**Description**
Review question	**What is the clinical /cost effectiveness of nicorandil for the management of anginal symptoms?**
Population	Adults with a diagnosis of stable angina including people with diabetes, South Asians, women, minimal coronary heart disease. Patients who have recurrence of anginal symptoms following revascularisation.
Intervention	Potassium channel activator: • Nicorandil
Comparison	In patients taking or not taking background therapies (same baseline combinations in both arms), Nicorandil vs. placebo Nicorandil vs. other antianginal monotherapy: • Beta blockers • CCB • LA nitrates

	• ivabradine • ranolazine • trimetazidine
Outcomes	<u>Mortality</u> @ longest available evaluation time point (preferred 5yr, 10 yr) *Preferred outcomes:* • All cause mortality • Cardiac mortality *Other outcomes:* • Cardiovascular mortality <u>Angina frequency</u> @ longest available evaluation time point (preferred 1yr, 5yr, 10yr) *Preferred outcomes*: • Angina incidence reported in diaries • GTN usage • <u>Exercise tolerance</u> (based on repeat of baseline ETT at a min of 3month follow up) *Preferred outcomes :* • Change in total exercise time *Other outcomes:* • Change in time to ST depression • Change in time to onset of symptoms • Change in time to stopping exercise • Change in workload <u>Major cardiac events</u> @ longest available evaluation time point (preferred 1yr, 5yr, 10yr) *Preferred outcome:* • Nonfatal MI *Other outcomes:* • Acute coronary syndrome Combinations of nonfatal MI, unstable angina, acute coronary syndrome, heart failure <u>Hospitalisation</u> @ 6m -1yr <u>Revascularisation</u> @ 1yr, 5yr, 10yr if available <u>Quality of Life</u> eg EQ-5D, SF-36, HAD, etc @ longest available evaluation timepoint (preferred 1y, 5y, 10y) <u>Adverse events</u>

Search strategy	The databases to be searched are Medline, Embase, The Cochrane Library, CINAHL Randomised controlled trials (RCTs) will be considered. If no RCTs are found for certain outcomes such as adverse events, well conducted cohort studies and observational studies may also be considered. Studies will be restricted to English language only No date restriction will be applied. Databases will be searched from their date of origin
The review strategy	*Preferred:* • Double blind RCTs • Minimum number of participants n=50 • >60% patients with stable angina • 3 months follow up • Adverse event data to be sourced from RCTs only

Review Protocol – Ivabradine and Ranolazine	
Component	**Description**
Review question	**What is the clinical /cost effectiveness of newer drugs for the management of angina?**
Population	• Adults with a diagnosis of stable angina including people with diabetes, South Asians, women, minimal coronary heart disease .
Intervention	• Ivabradine • ranolazine
Comparison	In patients taking or not taking background therapies (same baseline combinations in both arms), ivabradine vs. placebo ivabradine vs. other antianginal monotherapy (alone or in combination): • Beta blockers • CCB • LA nitrates • nicorandil • ranolazine ranolazine vs. placebo ranolazine vs. other antianginal monotherapy (alone or in combination):

	• Beta blockers • CCB • LA nitrates • nicorandil • ivabradine
Outcomes	Mortality @ longest available evaluation timepoint (preferred 5yr, 10 yr) *Preferred outcomes:* • All cause mortality • Cardiac mortality *Other outcomes:* • Cardiovascular mortality Angina frequency @ longest available evaluation timepoint (preferred 1yr, 5yr, 10yr) *Preferred outcomes:* • Angina incidence reported in diaries • GTN usage Angina severity @ longest available evaluation timepoint (preferred 1yr, 5yr, 10yr, not below 3m) • CCS score Exercise tolerance (based on repeat of baseline ETT at a min of 3m follow up) *Preferred outcomes:* • Change in total exercise time *Other outcomes:* • Change in time to ST depression • Change in time to onset of symptoms • Change in time to stopping exercise • Change in workload Major cardiac events @ longest available evaluation timepoint (preferred 1yr, 5yr, 10yr) *Preferred outcome:* • Nonfatal MI *Other outcomes:* • Acute coronary syndrome Combinations of nonfatal MI, unstable angina, acute coronary syndrome, heart failure • Hospitalisation @ 6m -1yr *Revascularisation* @ 1yr, 5yr, 10yr if available

	Quality of Life eg EQ-5D, SF-36, HAD, etc @ longest available evaluation timepoint (preferred 1y, 5y, 10y) Adverse events
Search strategy	The databases to be searched are Medline, Embase, The Cochrane Library, CINAHL Randomised controlled trials (RCTs) will be considered. If no RCTs are found for certain outcomes such as adverse events, well conducted cohort studies and observational studies may also be considered. Studies will be restricted to English language only No date restriction will be applied. Databases will be searched from their date of origin
The review strategy	*Preferred:* • Double blind RCTs • Minimum number of participants n=50 • >60% patients with stable angina • 3 month follow up • Adverse event data to be sourced from RCTs only

Review Protocol –Drug therapy vs Revascularisation	
Component	**Description**
Review question	In adults with stable angina, what is the clinical/cost effectiveness of revascularisation techniques versus optimal medical treatment to alleviate angina symptoms and to improve long term outcomes?
Population	Adults with a diagnosis of stable angina Subgroups: • diabetes, South Asians, women, • Number of vessels – single, double, or triple vessel coronary artery disease, (with or with not involving proximal left anterior descending (LAD) artery) • Left main stem disease (LMS) • LV function • Prior revascularisation
Intervention	PCI (includes coronary angioplasty and stents), CABG
Comparison	Optimal medical treatment

Outcomes	Exercise tolerance @ 6 months and longer Mortality @ longest available evaluation time point (preferred 5yr, 10 yr) Preferred outcomes: • All cause mortality • Cardiac mortality Other outcomes: • Cardiovascular mortality Angina frequency/severity *Preferred outcomes:* • Angina incidence reported in diaries • GTN usage • CCS score Major cardiac events @ longest available evaluation time point (preferred 1yr, 5yr, 10yr) *Preferred outcome:* • Nonfatal MI Hospitalisation @ 6m and longer Revascularisation @ 1yr, 5yr, 10yr if available Quality of Life e.g. EQ-5D, SF-36, HAD, etc @ longest available evaluation time point (preferred 1y, 5y, 10y)
Search strategy	The databases to be searched are Medline, Embase, The Cochrane Library, CINAHL Randomised controlled trials (RCTs) will be considered form 1975. (n=50) If no evidence available from RCTs only then Cohort studies will be considered from 1999 > 2000 patients (outcomes >1 year) Studies will be restricted to English language only Studies will be restricted to English language only No date restriction will be applied. Databases will be searched from their date of origin
Search terms	Myocardial/ coronary revascularization (1) **PCI** /percutaneous coronary intervention (coronary, balloon) angioplasty PCTA/ percutaneous transluminal coronary angioplasty coronary artery balloon dilation/dilatation (coronary, drug-eluting or bare metal) stent

	2) CABG, coronary artery bypass graft(ing)/ surgery /CAGS aortocoronary bypass/ACB
The review strategy	• Double blind RCTs • Minimum N=50 • >60% stable angina • Adverse event data to be sourced from RCTs only

Review Protocol – Revascularisation	
Component	**Description**
Review question	**In adults with stable angina, what is the clinical/cost effectiveness of revascularisation techniques to alleviate angina symptoms and to improve long term outcomes?**
Population	Adults with a diagnosis of stable angina Subgroups: • diabetes, South Asians, women, • Number of vessels – single, double, or triple vessel coronary artery disease, (with or with not involving proximal left anterior descending (LAD) artery) • Left main stem disease (LMS) • LV function • Prior revascularisation
Intervention	PCI (includes coronary angioplasty and stents)
Comparison	CABG
Outcomes	Exercise tolerance @ 6 months and longer Mortality @ longest available evaluation time point (preferred 5yr, 10 yr) Preferred outcomes: All cause mortality • Cardiac mortality Other outcomes: • Cardiovascular mortality Angina frequency/severity *Preferred outcomes:* • Angina incidence reported in diaries • GTN usage • CCS score (Angina functional class)

	Major cardiac events @ longest available evaluation time point (preferred 1yr, 5yr, 10yr) *Preferred outcome:* • Nonfatal MI • MI Hospitalisation @ 6m and longer Revascularisation @ 1yr, 5yr, 10yr if available Quality of Life e.g. EQ-5D, SF-36, HAD, etc @ longest available evaluation time point (preferred 1y, 5y, 10y)
Exclusion	Vineberg procedure
Search strategy	The databases to be searched are Medline, Embase, The Cochrane Library, CINAHL Randomised controlled trials (RCTs) will be considered form 1975. (n=50) If no evidence available from RCTs only then Cohort studies will be considered from 1999. (> 2000 patients , outcomes >1 year) Studies will be restricted to English language only
Search terms	Myocardial/coronary revascularization (1) **PCI** /percutaneous coronary intervention (coronary, balloon) angioplasty PCTA/ percutaneous transluminal coronary angioplasty coronary artery balloon dilation/dilatation (coronary, drug-eluting or bare metal) stent **2) CABG**, coronary artery bypass graft(ing)/ surgery /CAGS aortocoronary bypass/ACB
The review strategy	• RCTs • Minimum N=50 • >60% stable angina • Adverse event data to be sourced from RCTs only

Review Protocol – Secondary prevention - Aspirin and Clopidogrel	
Component	**Description**
Review question	**In adults with angina, what is the clinical/cost effectiveness of aspirin or clopidogrel to alleviate angina symptoms and to improve long term outcomes?**
Population	• Adults with a diagnosis of stable angina including people with diabetes, South Asians, women, minimal coronary heart disease
Intervention	(1)Aspirin (acetylsalicylic acid) + standard antianginal drugs (2) Clopidogrel, ticlopidine + standard antianginal drugs
Comparison	(1) and (2) Placebo or no treatment + standard antianginal drugs
Outcomes	Mortality @ longest available evaluation timepoint (preferred 5yr, 10 yr) Preferred outcomes • All cause mortality • Cardiac mortality Other outcomes: • Cardiovascular mortality Angina frequency/severity @ longest available evaluation timepoint (preferred 1yr, 5yr, 10yr, not below 3 months) *Preferred outcomes:* • Angina incidence reported in diaries • GTN usage • CCS score Major cardiac events @ longest available evaluation timepoint (preferred 1yr, 5yr, 10yr) *Preferred outcome:* • Nonfatal MI Hospitalisation @ 6months -1yr Revascularisation @ 1yr, 5yr, 10yr if available Quality of Life eg EQ-5D, SF-36, HAD, etc @ longest available evaluation timepoint (preferred 1y, 5y, 10y)

Search strategy	The databases to be searched are Medline, Embase, The Cochrane Library, CINAHL Randomised controlled trials (RCTs) will be considered. If no RCTs are found for certain outcomes such as adverse events, well conducted cohort studies and observational studies may also be considered. Studies will be restricted to English language only No date restriction will be applied. Databases will be searched from their date of origin
The review strategy	• Double blind RCTs • Minimum N=200 (consider studies with smaller sample size if large numbers are not available) • >60% stable angina • Adverse event data to be sourced from RCTs only

Review Protocol – Secondary prevention - Statins	
Component	**Description**
Review question	**What is the clinical /cost effectiveness of using statin therapy in patients with normal coronary arteries (syndrome X)?**
Population	Patients with typical symptoms of angina and minimal coronary heart disease
Intervention	Statins (HMG CoA reductase inhibitors) atorvastatin, fluvastatin, pravastatin, rosuvastatin, simvastatin (+/- standard anti-anginal treatment)
Comparison	Placebo or no treatment **(**+/- standard anti-anginal treatment)
Outcomes	Mortality @ longest available evaluation timepoint (preferred 5yr, 10 yr) Preferred outcomes: • All cause mortality • Cardiac mortality Other outcomes: • Cardiovascular mortality Angina frequency/severity *Preferred outcomes:* • Angina incidence reported in diaries • GTN usage • CCS score Major cardiac events @ longest available evaluation timepoint

	(preferred 1yr, 5yr, 10yr) *Preferred outcome:* • Nonfatal MI Hospitalisation @ 6m -1yr Revascularisation @ 1yr, 5yr, 10yr if available Quality of Life eg EQ-5D, SF-36, HAD, etc @ longest available evaluation timepoint (preferred 1y, 5y, 10y)
Search strategy	The databases to be searched are Medline, Embase, The Cochrane Library, CINAHL Randomised controlled trials (RCTs) will be considered. If no RCTs are found for certain outcomes such as adverse events, well conducted cohort studies and observational studies may also be considered. Studies will be restricted to English language only No date restriction will be applied. Databases will be searched from their date of origin
The review strategy	• Double blind RCTs • Minimum N=200 (consider studies with smaller sample size if large numbers are not available) • >60% stable angina • Adverse event data to be sourced from RCTs only

Review Protocol – Secondary prevention - ACE inhibitors and ARBs	
Component	**Description**
Review question	**What is the clinical /cost effectiveness of Ace inhibitors or ARBs for the management of angina?**
Population	• Adults with a diagnosis of stable angina • including people with diabetes, South Asians, women, minimal coronary heart disease
Intervention	(1) ACE inhibitors (in addition to standard anti-anginal treatment) captopril, cilazapril, enalapril, fosinopril, imidapril, lisinopril, moexipril, perindopril, quinapril, ramipril, trandolapril (2) ARBs (in addition to standard anti-anginal treatment) candasartan, valsartan, losartan, irbesartan, eprosartan, olmesartan, telmisartan
Comparison	Standard anti-anginal treatment (without ACE/without ARB)

Outcomes	Mortality @ longest available evaluation timepoint (preferred 5yr, 10 yr) Preferred outcomes: • All cause mortality • Cardiac mortality Other outcomes: • Cardiovascular mortality Angina frequency/severity *Preferred outcomes:* • Angina incidence reported in diaries • GTN usage • CCS score Exercise tolerance (based on repeat of baseline ETT at a min of 3m follow up) *Preferred outcomes:* • Total exercise time Major cardiac events @ longest available evaluation time point (preferred 1yr, 5yr, 10yr) *Preferred outcome:* • Nonfatal MI Hospitalisation @ 6months -1yr Revascularisation @ 1yr, 5yr, 10yr if available Quality of Life eg EQ-5D, SF-36, HAD, etc @ longest available evaluation timepoint (preferred 1y, 5y, 10y)
Search strategy	The databases to be searched are Medline, Embase, The Cochrane Library, CINAHL. Randomised controlled trials (RCTs) will be considered. If no RCTs are found for certain outcomes such as adverse events, well conducted cohort studies and observational studies may also be considered. Studies will be restricted to English language only No date restriction will be applied. Databases will be searched from their date of origin
The review strategy	For longer term outcomes (> 1 year) • Double blind RCTs • Minimum N=200 (consider smaller studies if large numbers not available) • >60% stable angina

	• Adverse event data to be sourced from RCTs only

Review Protocol –Risk tables, equations, engines, models or scoring systems for prognosis	
Component	**Description**
Review question	**In adults with stable angina which tables, equations, engines, models or scoring systems are most reliable/effective for prognostic-risk stratification in prediction of adverse cardiac outcomes?**
Population	Adults with a diagnosis of stable angina Subgroups: • diabetes, South Asians, women
Intervention	Risk tables, equations, engines, models or scoring systems <u>Possible clinical variables:*</u> Age Gender Hypertension Diabetes mellitus Previous MI Heart rate Smoking history Current drug therapy Body Mass Index Waist circumference ECG *additional clinical variables will be considered as defined risk model/engine/scoring system in the study.
Outcomes	Mortality • All cause mortality • Cardiac mortality • Cardiovascular mortality Major cardiac events *Preferred outcome:* • Nonfatal MI Hospitalisation Revascularisation
Exclusion	-

Search strategy	The databases to be searched are Registry databases, Medline, Embase, The Cochrane Library, CINAHL Studies will be restricted to English language only No date restriction will be applied. Databases will be searched from their date of origin
Search terms	Scoring systems/ tools/ clinical assessment/criteria comorbidities (hypertension/diabetes/MI/ smoking) age/gender/heart rate/ BMI AND (risk OR prognosis)
The review strategy	▪ Cohort studies and large RCT's ▪ Minimum participants, N=200 (preferred >500) ▪ >60% patients with stable angina

Review Protocol –Incremental value/effectiveness of anatomical/functional tests for prognosis	
Component	**Description**
Review question	**In adults with stable angina what is the INCREMENTAL value/effectiveness of anatomical/functional tests for prognostic risk stratification in prediction of adverse cardiac outcomes?**
Population	Adults with a diagnosis of stable angina Subgroups: • diabetes, South Asians, women,
Intervention	**Anatomical/functional tests** ➢ Exercise ECG / exercise tolerance test / exercise stress test / stress ECG. ➢ Stress echocardiography/exercise, dobutamine, dipyridamole, adenosine- stress echocardiography. ➢ Stress myocardial perfusion imaging/ MPS/ myocardial perfusion scintigraphy / exercise thallium MPS. ➢ MPS using single photon emission CT (SPECT). ➢ Stress magnetic resonance imaging / stress CMR / adenosine, dipyridamole -stress perfusion imaging / dobutamine -stress induced motion wall abnormalities. ➢ Computed tomography CT / CT coronary angiography / multi slice CT, multidetector CT / CT coronary angiography / CAT ➢ Ca scoring , coronary calcium scoring

	➢ Electron beam CT (EBCT). ➢ Coronary Angiography
Comparison	• Clinical assessment
Outcomes	Mortality • All cause mortality • Cardiac mortality • Cardiovascular mortality Major cardiac events *Preferred outcomes:* • MI • Nonfatal MI Hospitalisation revascularisation
Search strategy	The databases to be searched are Registry databases, Medline, Embase, The Cochrane Library, CINAHL Studies will be restricted to English language only No date restriction will be applied. Databases will be searched from their date of origin
Search terms	 Exercise tolerance test Stress echo/stress perfusion MPS/SPECT MRI/CMR/STRESS MRI CT /CAT/Cardiac CT/Coronary CT coronary angiography AND Prognosis
The review strategy	▪ Cohort studies and large RCT's ▪ Minimum participants, N=100 (preferred at least >500) ▪ >60% patients with stable angina

Review Protocol –Cardiac rehabilitation programmes	
Component	**Description**
Review question	**What is the clinical/cost effectiveness and safety of cardiac rehabilitation programmes for patients with stable angina?**
Population	Adults with a diagnosis of stable angina • including people with diabetes, South Asians, women, minimal coronary heart disease

Intervention	• Exercise training interventions • Psychological interventions • Behavioral interventions • Cognitive Behavioral therapy • health education interventions • Combinations which include exercise (Comprehensive i.e., Exercise training in addition to psychological, behavioral, cognitive, health education interventions).
Comparison	Standard care/usual medical care as defined by the study
Outcomes	Improvement in Anginal symptoms- Angina frequency (No. of anginal attacks) Nitroglycerin consumption Mortality @ longest available evaluation time point (preferred 5yr, 10 yr) Preferred outcomes: • All cause mortality • Cardiac mortality Other outcomes: • Cardiovascular mortality Exercise tolerance (based on repeat of baseline ETT at a min of 3m follow up) *Preferred outcomes:* • Total exercise time Major cardiac events @ longest available evaluation time point (preferred 1yr, 5yr, 10yr) *Preferred outcome:* • Nonfatal MI Hospitalisation @ 6m -1yr Revascularisation @ 1yr, 5yr, 10yr if available Quality of Life eg EQ-5D, SF-36, HAD, etc @ longest available evaluation timepoint (preferred 1y, 5y, 10y) Adverse events
Search strategy	The databases to be searched are, Medline, Embase, The Cochrane Library, CINAHL, Registry databases. Cohort studies will be considered if no RCT evidence available. Studies will be restricted to English language only No date restriction will be applied. Databases will be searched from their date of origin

Search terms	Exercise programmes/ therapy patient education/ self management / self care programmes CBT/ coping strategies/ “angina plan” Psychological support/ counselling
The review strategy	• RCT’s • Minimum N=50 • >60% stable angina

Review Protocol – Life style advice

Component	Description
Review question	**What is the clinical /cost effectiveness of angina specific life style advice for reducing symptoms, morbidity, mortality and improving quality of life in stable angina patients?**
Population	Adults with a diagnosis of stable angina Subgroups: • diabetes, South Asians, women,
Intervention	Programmes specifically for angina patients which modify lifestyle/CVD risk factors including • Diet (including folic acid, vitamin E, C, beta carotene supplements, Omega 3-acid ethyl esters, Mediterranean diet, low saturated diet, low glycemic diet, fruit and vegetables, fish diet) • Physical activity
Comparison	No lifestyle changes
Outcomes	<u>Exercise tolerance</u> <u>Mortality</u> @ longest available evaluation time point (preferred 5yr, 10 yr) Preferred outcomes: • All cause mortality • Cardiac mortality Other outcomes: • Cardiovascular mortality <u>Angina frequency/severity</u> @ longest available evaluation time point (preferred 1yr, 5yr, 10yr) *Preferred outcomes:* • Angina incidence reported in diaries • GTN usage • CCS score

	Major cardiac events @ longest available evaluation time point (preferred 1yr, 5yr, 10yr) *Preferred outcome:* • Nonfatal MI Hospitalisation @ 6m and longer Revascularisation @ 1yr, 5yr, 10yr if available Quality of Life e.g. EQ-5D, SF-36, HAD, etc @ longest available evaluation time point (preferred 1y, 5y, 10y)
Exclusion	-
Search strategy	The databases to be searched are Medline, Embase, The Cochrane Library, CINAHL . Randomised controlled trials (RCTs) will be preferred. Cohort studies will be considered if no RCT evidence is available. Studies will be restricted to English language only
Search terms	Food/ Diet/ diet therapy Alcohol/drinking behaviour Dietary/vitamin supplements Smoking/tobacco use cessation Weight loss/management NB exercise is covered in REHAB question
The review strategy	• RCTs • Minimum N=50 • >60% stable angina

Review Protocol – Angina specific specialised pain interventions	
Component	**Description**
Review question	**What is the clinical/cost effectiveness of (angina specific) specialised pain interventions in patients with stable angina?**
Population	1. Adults with a diagnosis of stable angina • including people with diabetes, South Asians, women, minimal coronary heart disease 2. Refractory angina
Intervention	Pain management • TENS (Transcutaneous electric nerve stimulation), • Spinal cord stimulation (NICE TA),

	• Cognitive Behavioral Therapy, • Temporary or destructive sympathectomy, • Analgesics (including opioids – oral, transdermal, epidural, transthecal.) • Myocardial laser (percutaneous or transmyocardial) (NICE TA) • EECP (Enhanced external counter pulsation) • Acupuncture
Comparison	• Head to head comparison of pain interventions • Compared to no treatment (no angina specific pain intervention)
Outcomes	<u>Improvement in Anginal symptoms-</u> Angina frequency (No. of anginal attacks) Nitroglycerin consumption <u>Mortality</u> @ longest available evaluation time point (preferred 5yr, 10 yr) Preferred outcomes: • All cause mortality • Cardiac mortality Other outcomes: • Cardiovascular mortality <u>Exercise tolerance</u> (based on repeat of baseline ETT at a min of 3m follow up) *Preferred outcomes:* • Total exercise time <u>Major cardiac events</u> @ longest available evaluation time point (preferred 1yr, 5yr, 10yr) *Preferred outcome:* • Nonfatal MI <u>Hospitalisation</u> @ 6m -1yr <u>Revascularisation</u> @ 1yr, 5yr, 10yr if available <u>Quality of Life</u> eg EQ-5D, SF-36, HAD, etc @ longest available evaluation timepoint (preferred 1y, 5y, 10y) Adverse events

Search strategy	The databases to be searched are, Medline, Embase, The Cochrane Library, CINAHL, Registry databases. Cohort studies will be considered if no RCT evidence available. Studies will be restricted to English language only No date restriction will be applied. Databases will be searched from their date of origin
Search terms	TENS/transcutaneous nerve stimulation Spinal cord stimulation Sympathectomy Acupuncture EECP/ enhanced external counterpulsation Myocardial laser CBT Analgaesics (oral, transdemal, epidural, transthecal routes) NSAIDS/ opioids/ -Others
The review strategy	• RCT's • Minimum N=50 • >60% stable angina • Cohort studies (n>100)

Review Protocol – Syndrome X	
Component	**Description**
Review question	**What is the clinical /cost effectiveness of the following drugs for the management of Syndrome X (people with stable angina symptoms and normal coronary arteries):** **BB, nitrates, CCB, ACE inhibitors, ARBs, Nicorandil, Ranolazine, Ivabradine, Aspirin?**
Population	All adults with a diagnosis of syndrome X
Intervention	BB, nitrates, CCB, ACEs , ARBs, Nicorandil, Ranolazine, Ivabradine, Aspirin
Comparison	BB, nitrates, CCB, ACEs , ARBs, Nicorandil, Ranolazine, Ivabradine, Aspirin
Outcomes	Immediate improvement in exercise tolerance – within 30 mins of intervention *Preferred outcome:* • Change in total exercise time *Other outcomes:* • Change in time to ST depression

	• Change in time to onset of symptoms • Change in time to stopping exercise • Change in workload <u>Frequency and/or severity of angina</u> <u>Important adverse events</u>
Search strategy	The databases to be searched are Medline, Embase, The Cochrane Library, CINAHL Randomised controlled trials (RCTs) will be considered. If no RCTs are found for certain outcomes such as adverse events, well conducted cohort studies and observational studies may also be considered. Studies will be restricted to English language only No date restriction will be applied. Databases will be searched from their date of origin
The review strategy	*Preferred:* • Double blind RCTs • Minimum number of participants n=50 (or 25 for cross-over studies) • Adverse event data to be sourced from RCTs only

Review Protocol – Health Economics	
Objectives	The aim is to identify economic studies relevant to the review questions set out above.
Criteria	Populations, interventions and comparators as specified in the review protocols above. Must be a relevant economic study design (cost-utility analysis, cost-benefit analysis, cost-effectiveness analysis, cost-consequence analysis, comparative cost analysis).
Search strategy	See Appendix C
The review strategy	Each study is assessed using the NICE economic evaluation checklist – NICE (2009) Guidelines Manual, Appendix H. Inclusion/exclusion criteria • If a study is rated as both 'Directly applicable' and 'Minor limitations' (using the NICE economic evaluation checklist) then it should be included in the guideline. An evidence table should be completed and it should be included in the economic profile. • If a study is rated as either 'Not applicable' or 'Very serious limitations' then it should be excluded from the guideline. It should not be included in the economic profile and there is no need to include an evidence table. • If a study is rated as 'Partially applicable' and/or 'Potentially serious limitations' then there is discretion over whether it should be included. The health economist should make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the GDG if required. The ultimate aim being to include studies that are helpful for decision making in the context of the guideline. Where exclusions occur on this basis, this should be noted in the relevant section of the guideline with references. Also exclude: • unpublished reports unless submitted as part of the call for evidence • abstract-only studies • letters • editorials • reviews of economic evaluations • foreign language articles Where there is discretion

	The health economist should be guided by the following hierarchies. Setting: 1. UK NHS 2. OECD countries with predominantly public health insurance systems (e.g. France, Germany, Sweden) 3. OECD countries with predominantly private health insurance systems (e.g. USA, Switzerland) 4. Non-OECD settings (always 'Not applicable') Economic study type: 1. Cost-utility analysis 2. Other type of full economic evaluation (cost-benefit analysis, cost-effectiveness analysis, Cost-consequence analysis) 3. Comparative cost analysis 4. Non-comparative cost analyses including cost of illness studies (always 'Not applicable') Year of analysis: • The more recent the study, the more applicable it is Quality of effectiveness data used in the economic analysis: • The more closely the effectiveness data used in the economic analysis matches with the studies included for the clinical review the more useful the analysis will be to decision making for the guideline.