Appendix B

CLINICAL QUESTIONS – STABLE ANGINA

Questions	Population (and subgroups)	Intervention	Comparison	Outcomes
Q1) What is the clinical /cost effectiveness of nicorandil for the management of angina? 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	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.	Potassium channel activator: • Nicorandil	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	Note: some shorter term outcomes such as ECG changes included in newer drugs Mortality @ longest available evaluation time point (preferred 5yr, 10 yr) Preferred outcomes : All cause mortality Cardiac mortality Other outcomes: Cardiovascular mortality Angina frequency @ longest available evaluation time point (preferred 1yr, 5yr, 10yr) Preferred outcomes : Angina incidence reported in diaries GTN usage Angina severity @ longest available

Questions	Population (and subgroups)	Intervention	Comparison	Outcomes
				evaluation time point (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 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) Adverse events

Questions	Population (and subgroups)	Intervention	Comparison	Outcomes
Q2) What is the clinical /cost effectiveness **of short acting drugs for the management of anginal symptoms?** Preferred : Double blind RCTs Minimum n=50 >60% stable angina Adverse event data to be sourced from RCTs only	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.	Short acting nitrate by buccal, lingual or sublingual administration Glyceryl trinitrate – tablet, spray •Nifedipine capsule by sublingual/buccal administration	• Nitrate spray vs. nitrate tablet • Nifedipine vs placebo • Nifedipine vs nitrate spray • Nifedipine vs nitrate tablet	**Note: these outcomes are primarily short-term 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 Frequency of angina (and prophylaxic use) Preferred outcomes: Time to relief of pain Incidence of angina post-intervention Others Pain severity Duration of pain

				important adverse events (headache and syncope)

Q 3) What is the clinical /cost effectiveness of **newer drugs for the management of angina**? 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	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.	Ivabradine Ranolazine	Placebo CCB B blockers Nitrates Combinations Placebo CCB B blockers Nitrates Combinations	**Note: some shorter term outcomes such as ECG changes included in newer drugs** Mortality @ longest available evaluation time point (preferred 5yr, 10 yr) Preferred outcomes : All cause mortality Cardiac mortality Other outcomes: Cardiovascular mortality Angina frequency @ longest available evaluation time point (preferred 1yr, 5yr, 10yr) Preferred outcomes : Angina incidence reported in diaries GTN usage

				Exercise tolerance Preferred outcomes : Change in total exercise time 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) Adverse events

<table>
<tr>
<td>Q4) What is the comparative clinical /cost effectiveness of standard antianginal drugs (calcium channel blockers, long acting nitrates) for the management of angina?

Preferred :
Double blind RCTs
Minimum n=50
>60% stable angina
Minimum Follow Up = 3m
Adverse event data to be sourced from RCTs only</td>
<td>Adults with a diagnosis of stable angina

including people with diabetes, South Asians, women, minimal coronary heart disease</td>
<td colspan="2">
<table>
<tr><td colspan="2">What is best drug to use first?</td></tr>
<tr><td>B blocker</td><td>CCB</td></tr>
<tr><td colspan="2">Are 2 drugs better than one?</td></tr>
<tr><td>B blocker</td><td>B blocker+ CCB</td></tr>
<tr><td>CCB</td><td>B blocker + CCB</td></tr>
<tr><td colspan="2">What is benefit of adding long acting nitrate?</td></tr>
<tr><td>B blocker + CCB</td><td>B Blocker + nitrate</td></tr>
<tr><td>B blocker + CCB</td><td>B blocker + CCB + nitrate</td></tr>
<tr><td>CCB</td><td>CCB + nitrates</td></tr>
<tr><td>B blocker</td><td>CCB + nitrates</td></tr>
<tr><td>CCB</td><td>B Blocker + nitrate</td></tr>
<tr><td>CCB + B blocker</td><td>CCB+ nitrate</td></tr>
<tr><td colspan="2">

<u>Beta blockers</u>
atenolol , propranolol, bisoprolol, metoprolol, nadolol,

<u>Calcium channel blockers</u>
amlodipine, diltiazem, felodipine, nifedipine, verapamil)

<u>Long acting nitrates</u>
Isosorbide dinitrate
Isosorbide mononitrate</td></tr>
</table>
</td>
<td>Mortality all cause @ longest available evaluation time point (preferred 5yr, 10 yr)
Preferred outcomes :

Cardiac mortality @ longest available evaluation time point (preferred 5yr, 10 yr)

Angina frequency @ longest available evaluation time point (preferred 1yr, 5yr, 10yr)
Preferred outcomes :
Angina incidence reported in diaries
GTN usage

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</td>
</tr>
</table>

				evaluation timepoint (preferred 1y, 5y, 10y)

Q 5) What is the clinical/cost effectiveness of **aspirin or clopidogrel** to alleviate angina symptoms and to improve long term outcomes? Preferred: Double blind RCTs Minimum number of participants n=50 >60% patients with stable angina **Minimum 1yr follow up** Adverse event data to be sourced from RCTs only	Adults with a diagnosis of stable angina • including people with diabetes, South Asians, women, minimal coronary heart disease. .	(1) Aspirin (acetylsalicylic acid) + standard antianginal drugs (2) Clopidogrel, ticlopidine + standard antianginal drugs	Aspirin +standard anginal treatment vs. standard anginal treatment Clopidogrel ,ticlodipine+ standard anginal treatment vs. standard anginal treatment Aspirin + clopidogrel,ticlodipine + standard anginal treatment vs. standard anginal treatment	Mortality @ longest available evaluation time point (preferred 5yr, 10 yr) Preferred outcomes : All cause mortality Cardiac mortality Other outcomes: Cardiovascular mortality Major cardiac events @ longest available evaluation time point (preferred 1yr, 5yr, 10yr) Preferred outcome: Nonfatal MI Hospitalisation @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
Q 6) What is the clinical /cost effectiveness of **ACE inhibitors or ARBs** for the management of angina? Preferred: Double blind RCTs Minimum number of participants n=50 >60% patients with stable angina Minimum 1yr follow up Adverse event data to be sourced from RCTs only	Adults with a diagnosis of stable angina • including people with diabetes, South Asians, women, minimal coronary heart disease.	(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	ACE or ARB vs. Standard anti-anginal treatment (without ACE/without ARB)	Mortality @ longest available evaluation timepoint (preferred 5yr, 10 yr) Preferred outcomes : All cause mortality Cardiac mortality Other outcomes: Cardiovascular mortality Major cardiac events @ longest available evaluation timepoint (preferred 1yr, 5yr, 10yr) Preferred outcome: Nonfatal MI Hospitalisation @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) Adverse events
Q7) What is the clinical /cost effectiveness of using **statin therapy** in patients with normal coronary arteries (syndrome X)? Preferred: Double blind RCTs Minimum number of participants n=50 >60% patients with stable angina Minimum 1yr follow up Adverse event data to be sourced from RCTs only	For statins: Patients with typical symptoms of angina and minimal coronary heart disease .	Statins (HMG CoA reductase inhibitors) atorvastatin, fluvastatin, pravastatin, rosuvastatin, simvastatin (+/- standard anti-anginal treatment)	Placebo or no treatment (+/- standard anti-anginal treatment)	Mortality @ longest available evaluation time point (preferred 5yr, 10 yr) Preferred outcomes : All cause mortality Cardiac mortality Other outcomes: Cardiovascular mortality Major cardiac events @ longest available evaluation time point (preferred 1yr, 5yr, 10yr) Preferred outcome: Nonfatal MI Hospitalisation @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

Q 8) In adults with angina, what is the clinical/cost effectiveness of **revascularisation techniques** to alleviate angina symptoms and to improve long term outcomes? • RCTs • Minimum N=50 • >60% stable angina • Adverse event data to be sourced from RCTs only	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	PCI (includes coronary angioplasty and stents), CABG	PCI vs. CABG	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 @ longest available evaluation time point (preferred 1yr, 5yr, 10yr, not below 3 months) Preferred outcomes: • Angina incidence reported in diaries • GTN usage • CCS score

• Cohort studies N > 2000				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)

Q 9) What is the clinical/cost effectiveness of **revascularisation compared to pharmacotherapy** in stable angina?	Adults with a diagnosis of stable angina Subgroups: • diabetes, South Asians, women, • Number of	PCI , CABG	PCI vs. Medical therapy CABG vs. Medical therapy PCI +CABG vs.	exercise tolerance @ 6 months and longer Mortality @ longest available evaluation time point (preferred 5yr, 10 yr) Preferred outcomes:

RCTs Minimum N=50 >60% stable angina Adverse event data to be sourced from RCTs only Cohort studies N > 2000	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		Medical therapy	• All cause mortality • Cardiac mortality Other outcomes: • Cardiovascular mortality Angina frequency/severity @ longest available evaluation time point (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 time point (preferred 1yr, 5yr, 10yr) Preferred outcome: • Nonfatal MI Hospitalisation @ 6m and longer 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)

Q10) What is the clinical/cost effectiveness of **cardiac rehabilitation programmes** for patients with stable angina Threshold of reporting for all = angina patients> 60% of population	Adults with stable angina - including people with diabetes, South Asians minimal coronary heart disease and women?	• Exercise based cardiac rehabilitation programmes • Psychological interventions • Behavioural interventions • Cognitive interventions • Health education interventions. • Exercise training in addition to psychological, behavioural and/or health education interventions. (i.e. Comprehensive rehab programmes)	Standard care/usual medical care as defined by the study	Improvement in Angina symptoms- Frequency of angina Consumption of nitroglycerin All cause mortality, cardiac mortality, cardiovascular mortality @ 5yr, 10yr Frequency of angina, improvement in exercise tolerance e.g. 1m, 1yr, 5yr Major cardiac events – non fatal MI e.g. 1yr, 5yr Hospitalisation e.g. 1yr, 5yr, 10yr Revascularisation rates e.g. 5yr, 10yr Quality of Life (including anxiety and depression) e.g. EQ-5D, SF-36, HAD, etc @ 1yr, 5yr, 10 yr Adverse effects

Questions	Population (and subgroups)	Intervention	Comparison	Outcomes
11) Cardiac syndrome X	All adults with a diagnosis of syndrome X	BB, nitrates, CCB, ACEs , ARBs, Nicorandil, Ranolazine, Ivabradine, Aspirin	BB, nitrates, CCB, ACEs , ARBs, Nicorandil, Ranolazine, Ivabradine, Aspirin	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 Frequency and/or severity of angina (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)

Questions	Population (and subgroups)	Intervention	Comparison	Outcomes
12) Which **tables, equations, engines, models or scoring systems** are most effective for prognostic -risk stratification in prediction of adverse cardiac outcomes in adults with stable angina?	Adults with a diagnosis of stable angina – including people with diabetes, South Asians, women	Risk tables, equations, engines, models or scoring systems	Possible Clinical variables : Age Gender Hypertension Diabetes mellitus Previous MI Heart rate Smoking history Current drug therapy Body Mass Index Waist circumference ECG	All cause mortality, cardiac mortality, cardiovascular mortality, Major cardiac events – fatal MI, non fatal MI Hospitalisation *Look at Registry studies of people with Angina with prognosis purposes and risk scores.* *Cohort studies over 1000* *Large randomised trials patients.* *Look at – ACTION Score trial*

Q13) What is the INCREMENTAL value/effectiveness of **anatomical/functional tests** for prognostic risk stratification in prediction of adverse cardiac outcomes in adults with stable angina?	Adults with a diagnosis of stable angina – including people with diabetes, South Asians, women	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 perfusion imaging / stress induced motion wall abnormalities. -Magnetic resonance coronary angiography. -Computed tomography CT / CT coronary angiography /	Clinical assessment	All cause mortality, cardiac mortality, cardiovascular mortality, Major cardiac events –fatal MI, non-fatal MI Hospitalisation

		multi slice CT / CT coronary angiography / CAT -Ca scoring -Electron beam CT (EBCT). - Coronary angiography		

Q14) What is the clinical/cost effectiveness of **(angina specific) specialised pain interventions** in patients with stable angina?	Adults with diagnosed stable angina - including people with diabetes, South Asians, refractory angina, minimal coronary heart disease and women (Comment only - not to be reviewed) patients who have recurrence of anginal symptoms following revascularisation	Pain management TENS (Transcutaneous electric nerve stimulation), Spinal cord stimulation (NICE TA), Cognitive Behavioural Therapy, Temporary or destructive sympathectomy, Analgesics (inc opioids – oral, transdermal, epidural, transthecal.), Myocardial laser (percutaneous or transmyocardial) (NICE TA), EECP (Enhanced external	Treatment vs. no treatment Treatment vs. placebo Treatment A vs. treatment B	All cause mortality, cardiac mortality, cardiovascular mortality, @ 5yr, 10yr Frequency of angina, improvement in exercise tolerance (immediate relief, symptoms over longer period e.g. 5yr, 10yr) Major cardiac events – non fatal MI Procedural morbidity e.g. @ 1m, 1yr Hospitalisation e.g. 5yr, 10yr Revascularisation rates e.g. 5yr, 10yr

		counterpulsation) Acupuncture		Quality of Life e.g. EQ-5D, SF-36, HAD, etc @ 1yr, 5yr, 10yr Adverse events

Q15) What are the **education and information needs of adults with stable angina** to optimise their understanding of their diagnosis and of their participation in treatment decisions?	Adults with a diagnosis of stable angina including people with diabetes, South Asians, women, refractory angina, minimal coronary heart disease	Patient education/information interventions (including information on sexual activity, choice of drugs vs. revascularisation)	No comparison group. This is a question best answered using qualitative methods or studies with good validated survey methodology.	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

Q16) What is the clinical /cost effectiveness of **angina specific interventions to modify lifestyle/CVD risk factors to reduce symptoms, morbidity and mortality and improve quality of life** in angina patients?	Adults with stable angina - including people with diabetes, South Asians, refractory angina, minimal coronary heart disease and women?	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, plant sterols esters, low glycemic diet, fruit and vegetables, fish diet, high fibre diet) Physical activity Alcohol consumption Smoking cessation Weight management (*Any other life style factors to be included??)	No life style changes	All cause mortality, cardiac mortality, cardiovascular mortality @ 1yr, 5yr, 10yr Frequency of angina, improvement in exercise tolerance e.g. 1m, 1yr, 5yr Major cardiac events – non fatal MI e.g. 1yr, 5yr, 10yr Hospitalisation e.g. 1yr, 5yr, 10yr Revascularisation rates e.g. 1yr, 5yr, 10yr Quality of Life (including anxiety and depression) e.g. EQ-5D, SF-36, HAD, etc @ 1yr, 5yr, 10 yr Adverse effects