1 **Appendix I**

2 **Criteria for selecting high priority research recommendations**

3 *1.1   Addition of the newer anti-anginal drugs to CCB*

4   **Research question:**

5   What is the clinical and cost effectiveness of adding a newer anti-anginal drug
6   (nicorandil, ivabradine or ranolazine) to a calcium channel blocker for treating stable
7   angina?

8   **Why this is important:**

9   We do not know the clinical and cost effectiveness of adding a newer anti-anginal
10   drug to a calcium channel blocker in people with stable angina. We propose a
11   double-blind placebo-controlled randomised trial comparing the addition of a newer
12   anti-anginal drug to a calcium channel blocker with a calcium channel blocker alone in
13   people with stable angina whose symptoms are not being controlled. Endpoints would
14   include symptom severity, quality of life, long-term morbidity and mortality, and cost
15   effectiveness. The results of the trial would influence clinical practice and inform future
16   updates of key recommendations in this guideline.

17   Criteria for selecting high-priority research recommendations:

<u>Importance to patients or the population.</u> What would be the impact on the population of any new or altered guidance? (for example, acceptability to patients, quality of life, morbidity or disease prevalence, severity of disease or mortality).	It is important to find out the additional benefit that can be gained from using a newer anti-anginal agent with a Calcium Channel Blocker in patients with Angina because it may provide them with an alternative treatment that would alleviate the severity of their disease and a better quality of life.
<u>Relevance to NICE guidance</u> How would the answer to this question change future NICE guidance (that is, generate new knowledge and/or evidence)?	This knowledge will help in updating the NICE Guidance in the treatment of Stable Angina.
<u>Relevance to the NHS</u> What would be the impact on the NHS and (where relevant) the public sector of any new or altered guidance (for example, financial advantage, effect on staff, impact on strategic planning or service delivery)?	Providing a better control of Angina would also help in reducing the complications of the disease, GP and Hospital attendance, thereby saving the NHS unnecessary expenditure.
<u>National priorities</u>	This is very relevant to the CHD NHS

Is the question relevant to a national priority area (such as a national service framework or white paper)? The relevant document should be specified.	service Framework and to the current Stable Angina Guidance.
Current evidence base What are the problems with the current evidence base? (that is, why is further research required?) Reference should be made to the section of the full guideline that describes the current evidence base, including details of trials and systematic reviews.	Often newer agents can safely be added to B-Blockers. However, currently, there is no evidence of any trial that has been conducted to elucidate the benefit of adding one of the newer Anti-anginal drugs mentioned before, to a Calcium Channel Blocker.
Equality Does the research recommendation address equality issues? For example, does it focus on groups that need special consideration, or focus on an intervention that is not available for use by people with certain disabilities?	The proposed trial will focus on groups of patients with Angina in whom a second anti-anginal agent is needed and also on those in whom B-Blockers are not tolerated or contraindicated.
Study design It should also specify the most appropriate study design to address the proposed question(s). Primary research or secondary research (for example, systematic reviews) can be recommended.	This will be a primary research and should take the style of Double-blind RCT.
Feasibility Can the proposed research be carried out in a realistic timescale and at an acceptable cost? Are there any ethical or technical issues?	This proposed research can be carried out in 1-2 years at an acceptable cost with the help of the relevant pharmaceutical firms and has to comply with the ethical standards of research in the UK.
Other comments Any other important issues should be mentioned, such as potential funders or outcomes of previous attempts to address this issue or methodological problems. However, this is not a research protocol.	
Importance How important is the question to the overall guideline? The research recommendation should be categorised into one of the following	High Importance

categories of importance:

• High: the research is essential to inform future updates of key recommendations in the guideline

• Medium: the research is relevant to the recommendations in the guideline, but the research recommendations are not key to future updates

• Low: the research is of interest and will fill existing evidence gaps.

1.2 Interventional vs continuing medical management in patients with stable angina and demonstrable ischaemia on non-invasive testing

Research question:

Do people with stable angina and evidence of reversible ischaemia on non-invasive functional testing who are on optimal drug treatment benefit from routine coronary angiography with a view to revascularisation?

Why this is important:

Revascularisation has traditionally been offered to people with stable angina who have evidence of reversible ischaemia on non-invasive functional testing. Recent trials in people with stable angina (COURAGE, BARI-2D, MASS II) have not shown survival benefit from revascularisation compared with drug treatment. In the nuclear substudy of COURAGE (n = 314), PCI was shown to be more effective in treating ischaemia than optimal drug treatment, and in multivariate analyses reduction of ischaemia was associated with greater event-free survival. It is unclear, however, whether people on optimal drug treatment who have evidence of inducible ischaemia on non-invasive functional testing should routinely have coronary angiography and revascularisation. This question is particularly relevant for people who have responded adequately (say Canadian Cardiovascular Class 1 or 2) to optimal drug treatment and in whom, based on symptoms alone, revascularisation is not indicated. To answer this question we recommend a randomised trial of interventional management versus continued drug treatment in people with stable angina and myocardial ischaemia on non-invasive functional testing, with all-cause mortality and cardiovascular mortality as the primary endpoints.

1   Criteria for selecting high-priority research recommendations:

<u>Importance to patients or the population.</u> What would be the impact on the population of any new or altered guidance? (for example, acceptability to patients, quality of life, morbidity or disease prevalence, severity of disease or mortality).	Uncertainty remains, about whether decisions for cardiac catheterisation in patients on optimal medical treatment should be driven by symptoms alone or by the results of non-invasive ischaemia testing. Research is aimed to address this uncertainty
<u>Relevance to NICE guidance</u> How would the answer to this question change future NICE guidance (that is, generate new knowledge and/or evidence)?	Will inform future updates of key recommendations in the guideline
<u>Relevance to the NHS</u> What would be the impact on the NHS and (where relevant) the public sector of any new or altered guidance (for example, financial advantage, effect on staff, impact on strategic planning or service delivery)?	Identifying the optimal diagnostic procedures required prior to PCI can help optimise resource utilisation within the NHS and minimise variation in clinical practice and outcomes
<u>National priorities</u> Is the question relevant to a national priority area (such as a national service framework or white paper)? The relevant document should be specified.	.
<u>Current evidence base</u> What are the problems with the current evidence base? (that is, why is further research required?) Reference should be made to the section of the full guideline that describes the current evidence base, including details of trials and systematic reviews.	Recent trials that have recruited patients with stable angina (COURAGE, BARI-2D, MASS II), have failed to confirm survival benefit for revascularisation strategies compared with medical treatment. In the nuclear substudy of COURAGE, percutaneous intervention produced more effective resolution of ischaemia than optimal medical treatment but only 314 patients were recruited and risk-adjusted mortality was similar for the two groups.
<u>Equality</u> Does the research recommendation address equality issues? For example, does it focus on groups that need special consideration, or focus on an intervention that is not available for	

use by people with certain disabilities?	
Study design It should also specify the most appropriate study design to address the proposed question(s). Primary research or secondary research (for example, systematic reviews) can be recommended.	The question is particularly relevant in the group of patients that has responded adequately (say CCS class 1 or 2) to optimal medical treatment in whom revascularisation on symptomatic grounds is not indicated. To answer the question in this group we recommend a randomised trial of interventional versus continuing medical management in with all cause and cardiovascular mortality as the primary endpoints.
Feasibility Can the proposed research be carried out in a realistic timescale and at an acceptable cost? Are there any ethical or technical issues?	
Other comments Any other important issues should be mentioned, such as potential funders or outcomes of previous attempts to address this issue or methodological problems. However, this is not a research protocol.	
Importance How important is the question to the overall guideline? The research recommendation should be categorised into one of the following categories of importance: • High: the research is essential to inform future updates of key recommendations in the guideline • Medium: the research is relevant to the recommendations in the guideline, but the research recommendations are not key to future updates • Low: the research is of interest and will fill existing evidence gaps.	High importance.

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1.3   *Coronary anatomy investigations*

Research question:

In people with stable angina and multivessel disease (including left main stem [LMS] disease) whose symptoms are controlled on optimal drug treatment, would an initial treatment strategy of revascularisation be clinically and cost effective compared with continued drug treatment?

Why this is important:

Research is needed to determine whether early investigation and revascularisation can improve longer term survival. People with stable angina may be disadvantaged if they do not have tests to identify whether they have a higher risk profile for early cardiac death, which could be reduced by revascularisation. This disadvantage could be magnified when people who are deemed to fall into very high risk groups (for example, LMS stenosis > 50% in the MASS II trial) are excluded from randomised trials, resulting in the benefits of revascularisation being underestimated. We propose a randomised trial comparing an initial strategy of revascularisation (PCI or CABG) with an initial strategy of continued drug treatment in people with multivessel disease (including LMS disease) in whom revascularisation is not needed for symptom relief. The trial should use drug-eluting stents and wider inclusion criteria than BARI-2D and COURAGE.

Criteria for selecting high-priority research recommendations:

Importance to patients or the population. What would be the impact on the population of any new or altered guidance? (for example, acceptability to patients, quality of life, morbidity or disease prevalence, severity of disease or mortality).	Potentially improved survival, fewer myocardial infarctions, and fewer hospitalisations for repeat interventions
Relevance to NICE guidance How would the answer to this question change future NICE guidance (that is, generate new knowledge and/or evidence)?	Could significantly change the recommendations by encouraging earlier investigation or provide a reliable evidence base for not doing so.
Relevance to the NHS What would be the impact on the NHS and (where relevant) the public sector of any new or altered guidance (for example, financial advantage, effect on staff, impact on strategic planning or service delivery)?	Advancing the treatment of coronary artery disease to the highest international standards.
National priorities Is the question relevant to a national	Contributes to implementation of the NSF for Coronary Heart Disease

priority area (such as a national service framework or white paper)? The relevant document should be specified.	
Current evidence base What are the problems with the current evidence base? (that is, why is further research required?) Reference should be made to the section of the full guideline that describes the current evidence base, including details of trials and systematic reviews.	This question has not been formally addressed leaving a significant gap in the evidence base.
Equality Does the research recommendation address equality issues? For example, does it focus on groups that need special consideration, or focus on an intervention that is not available for use by people with certain disabilities?	Current practice for investigation of stable coronary disease is patchy and a reliable evidence base would improve equality of care
Study design It should also specify the most appropriate study design to address the proposed question(s). Primary research or secondary research (for example, systematic reviews) can be recommended.	A randomised study of patients in primary and secondary care whose symptoms are apparently adequately controlled with medication
Feasibility Can the proposed research be carried out in a realistic timescale and at an acceptable cost? Are there any ethical or technical issues?	No major stumbling blocks evident.
Other comments Any other important issues should be mentioned, such as potential funders or outcomes of previous attempts to address this issue or methodological problems. However, this is not a research protocol.	
Importance How important is the question to the overall guideline? The research recommendation should be categorised into one of the following categories of importance: • High: the research is essential to	High

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inform future updates of key recommendations in the guideline • Medium: the research is relevant to the recommendations in the guideline, but the research recommendations are not key to future updates • Low: the research is of interest and will fill existing evidence gaps.	

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1.4 Cardiac Rehabilitation

Research question:

Is an 8-week, comprehensive, multidisciplinary, cardiac rehabilitation service more clinically and cost effective for managing stable angina than current clinical practice?

Why this is important:

Cardiac rehabilitation programmes are an established treatment strategy for certain heart conditions, such as for people who have had a heart attack. However, there is no evidence to suggest that cardiac rehabilitation is clinically or cost effective for managing stable angina. Research to date has looked at short-term outcomes, such as a change in diet or exercise levels, but the effect on morbidity and mortality has not been studied. A randomised controlled trial is required to compare comprehensive cardiac rehabilitation with standard care in people with stable angina, with measures of angina severity (exercise capacity, angina frequency, use of a short-acting nitrate), and long-term morbidity and mortality as endpoints.

Criteria for selecting high-priority research recommendations:

<u>Importance to patients or the population.</u> What would be the impact on the population of any new or altered guidance? (for example, acceptability to patients, quality of life, morbidity or disease prevalence, severity of disease or mortality).	It would help optimise and standardise care for patients with stable angina and reduce variation. It would provide a structured comprehensive MDT service accessible to stable angina patients.
<u>Relevance to NICE guidance</u> How would the answer to this question change future NICE guidance (that is, generate new knowledge and/or evidence)?	There is no comprehensive evidence base currently.
<u>Relevance to the NHS</u> What would be the impact on the NHS	Identifying whether CR is clinically and cost effective for patients with stable

and (where relevant) the public sector of any new or altered guidance (for example, financial advantage, effect on staff, impact on strategic planning or service delivery)?	angina, will help determine pathways for stable angina patients that will standardise their care, and reduce variation.
National priorities Is the question relevant to a national priority area (such as a national service framework or white paper)? The relevant document should be specified.	The NSF for CHD was unable to clarify if CR was appropriate for stable angina patients; Consequently this research work could provide structure to National Frameworks.
Current evidence base What are the problems with the current evidence base? (that is, why is further research required?) Reference should be made to the section of the full guideline that describes the current evidence base, including details of trials and systematic reviews.	There is no evidence that evaluates the whole package that CR could potentially provide.
Equality Does the research recommendation address equality issues? For example, does it focus on groups that need special consideration, or focus on an intervention that is not available for use by people with certain disabilities?	Research can address equality issues e.g. evidence can minimise variation in the management and resulting outcomes for stable angina patients
Study design It should also specify the most appropriate study design to address the proposed question(s). Primary research or secondary research (for example, systematic reviews) can be recommended.	Previous studies that have looked at aspects of cardiac rehabilitation to angina patients, have been small, with only short term follow up. Therefore it is suggested that a Randomised Control Study, with follow up at 5 years, will help to address this gap. Sample groups should be greater than 100.
Feasibility Can the proposed research be carried out in a realistic timescale and at an acceptable cost? Are there any ethical or technical issues?	There is a large stable angina population across the UK as well as numerous establishments that currently provide CR services to stable angina patients.
Other comments Any other important issues should be mentioned, such as potential funders or outcomes of previous attempts to address this issue or methodological problems. However, this is not a	The University of Glamorgan has supported a similar research project that addressed the issue of Heart Failure and CR; they may consider supporting this research. The British Heart Foundation may be a

research protocol.	potential supporter
Importance How important is the question to the overall guideline? The research recommendation should be categorised into one of the following categories of importance: • High: the research is essential to inform future updates of key recommendations in the guideline • Medium: the research is relevant to the recommendations in the guideline, but the research recommendations are not key to future updates • Low: the research is of interest and will fill existing evidence gaps.	Medium to high importance.

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1.5 Patient Self-Management Plans

3 **Research question:**

4 What is the clinical and cost effectiveness of a self-management plan for people with
5 stable angina?

6 **Why this is important:**

7 Stable angina is a chronic condition. Evidence suggests that addressing people's
8 beliefs and behaviours in relation to angina may improve quality of life, and reduce
9 morbidity and use of resources. Self-management plans could include: educating
10 people with stable angina about the role of psychological factors in pain and pain
11 control; and teaching people self-management skills to modify cognitions, behaviours
12 and affective responses in order to control chest pain. These skills may include pacing
13 of physical activities, modifying stress using cognitive reframing and problem-solving
14 techniques, and relaxation training or mindfulness techniques. The proposed study is a
15 randomised controlled trial in primary care that would assess the clinical and cost
16 effectiveness of self-management plans. This research would inform future updates of
17 key recommendations in the guideline. Furthermore the research would be relevant to
18 a national priority area (National service framework for coronary heart disease [NSF
19 CHD] chapter 4: stable angina and chapter 7: cardiac rehabilitation) as well as the
20 Coalition White Paper 2010 (Equity and excellence: liberating the NHS) that
21 emphasize the importance of increasing people's choice and control in managing their
22 condition.

1 Criteria for selecting high-priority research recommendations:

<u>Importance to patients or the population.</u> What would be the impact on the population of any new or altered guidance? (for example, acceptability to patients, quality of life, morbidity or disease prevalence, severity of disease or mortality).	Improved quality of life Improved survival Less use of medication Reduced side effects of medication and coronary intervention(PCI and CABG)
<u>Relevance to NICE guidance</u> How would the answer to this question change future NICE guidance (that is, generate new knowledge and/or evidence)?	It would strengthen the evidence for such a plan. If cost effective it would need to be cheaper in resource terms than the status quo ie no effective self management plan in place
<u>Relevance to the NHS</u> What would be the impact on the NHS and (where relevant) the public sector of any new or altered guidance (for example, financial advantage, effect on staff, impact on strategic planning or service delivery)?	It should apply to all stable angina patients whether being seen in primary secondary or tertiary care
<u>National priorities</u> Is the question relevant to a national priority area (such as a national service framework or white paper)? The relevant document should be specified.	NSF CHD chapters 4 (stable angina) and chapter 7 (cardiac rehabilitation) Coalition White Paper 2010: Equity and excellence: Liberating the NHS: Putting patients and public first : We will put patients at the heart of the NHS, through an information revolution and greater choice and control: Shared decision-making will become the norm: no decision about me without me. Patients will have access to the information they want, to make choices about their care. They will have increased control over their own care records.

Current evidence base What are the problems with the current evidence base? (that is, why is further research required?) Reference should be made to the section of the full guideline that describes the current evidence base, including details of trials and systematic reviews.	No UK based studies No primary care based studies No RCTs
Equality Does the research recommendation address equality issues? For example, does it focus on groups that need special consideration, or focus on an intervention that is not available for use by people with certain disabilities?	Covers all patients
Study design It should also specify the most appropriate study design to address the proposed question(s). Primary research or secondary research (for example, systematic reviews) can be recommended.	RCT with health economics analysis
Feasibility Can the proposed research be carried out in a realistic timescale and at an acceptable cost? Are there any ethical or technical issues?	RCT in primary care
Other comments Any other important issues should be mentioned, such as potential funders or outcomes of previous attempts to address this issue or methodological problems. However, this is not a research protocol.	
Importance How important is the question to the overall guideline? The research recommendation should be categorised into one of the following categories of importance: • High: the research is essential to inform future updates of key recommendations in the guideline • Medium: the research is relevant to the recommendations in the guideline,	High

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| but the research recommendations are not key to future updates

• Low: the research is of interest and will fill existing evidence gaps. | |

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