NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Evaluation Pathway Programme assessment

Specification for manufacturer/sponsor submission of evidence

March 2010

Contents

List of tables and figures

Please include a list of all tables and figures here with relevant page references.

Instructions for manufacturers and sponsors

This is the specification for submission of evidence to the National Institute for Health and Clinical Excellence (NICE) as part of the Medical Technology Evaluation Programme assessment process. It shows manufacturers and sponsors what information NICE requires and the format in which it should be presented.

Those completing the template are asked to pay particular attention to Section 8.2 which describes arrangements for handling of information which NICE may be asked to treat in confidence.

Use of the specification and completion of appendices 1 to 13 (sections 7.1 to 7.13) are mandatory (when applicable), and the format should be followed whenever possible. Reasons for not following this format must be clearly stated. Sections that are not considered relevant should be marked 'N/A' and a reason given for this response. The specification should be completed with reference to the NICE document 'Evaluation Pathway Programme methods guide' (www.nice.org.uk). Users should see NICE's 'Evaluation Pathway Programme process guide' (www.nice.org.uk) for further details on some of the procedural topics referred to only briefly here.

If a submission is based on preliminary regulatory recommendations, the manufacturer or sponsor must advise NICE immediately of any variation between the preliminary and final approval.

A submission should be as brief and informative as possible. It is expected that the main body of the submission will not usually exceed **100 pages excluding the pages covered by the template**. Confine yourself to completing the response sections and appendices only. The submission should be sent to NICE electronically in Word or a compatible format, and not as a PDF file.

The submission must be a stand-alone document. Additional appendices may only be used for supplementary explanatory information that exceeds the level of detail requested, but that is considered to be relevant to the submission.

Appendices are not normally presented to the Medical Technology Advisory Committee. Any additional appendices should be clearly referenced in the body of the submission. **Appendices should not be used for core information that has been requested in the specification.** For example, it is not acceptable to attach a key study as an appendix and to complete the clinical-effectiveness section with ‘see appendix X’. Clinical study reports and protocols should not be submitted, but must be made available on request.

Studies should be identified by the first author or study ID, rather than by relying on numerical referencing alone (for example, ‘Study 123/Jones et al.[126]’ rather than ‘One study[126]’).

For information on submitting economic models, disclosure of information and equality and diversity, users should see ‘Related procedures for evidence submission’, section 8.

Section A – Decision problem

Section A is to be completed in conjunction with the Scope. Manufacturers and sponsors are requested to submit this section in advance of the full submission (for details on timelines, see the NICE document 'Evaluation Pathway Programme process guide' – www.nice.org.uk).

1 Description of technology under assessment

1.1 Give the brand name, approved name and details of any different versions of the same device.

Response

VeriQ. 4122, 4 flow, 1 doppler, 2 pressure, 2 ECG/aux channels

VeriQ 2011, 2 Flow, 1 Pressure, 1 ECG/aux channel

VeriQ 2111. 2 Flow, 1 Doppler, 1 Pressure, 1 ECG/aux channel

1.2 What is the principal mechanism of action of the technology?

Response

Device Description:
The VeriQ system incorporates several ultrasound modalities that can be used during a variety of surgical interventions. The system utilizes the well established technology of transit-time flow measurements to accurately measure blood flow in veins and arteries intraoperatively. The system also has the ability to connect other external physiological signals such as blood pressure, ECG and other auxiliary signals provided by other monitoring systems. The system is described in EU certificate of conformity as a "medical ultrasonic non-imaging flow meter system"

1.3 Does the technology have CE marking for the indications detailed in this submission? If so, give the date on which authorisation was received. If not, state current UK regulatory status, with relevant dates (for example, date of application and/or expected approval dates).

Response

Yes.

Received 2003 No. EU0211003.

1.4 Describe the main issues discussed by the regulatory organisation (preferably by referring to the (draft) assessment report (for example, CE marking)). If appropriate, state any special conditions attached to the marketing authorisation (for example, exceptional circumstances/conditions to the licence).

Response

There were no issues or special conditions.

1.5 What is the (anticipated) CE marking, including the indication for use.

Response

N/A – Already approved/issued.

1.6 Please provide details of all completed and ongoing studies from which additional evidence is likely to be available in the next 12 months for the indication being appraised.

Response

We are aware of none, neither are we instigating any.

1.7 If the technology has not been launched, please supply the anticipated date of availability in the UK.

Response

Launched 2004

1.8 Does the technology have regulatory approval outside the UK? If so, please provide details.

Response

Yes.

Australia	Licence no. 135092
China	SFDA (I)20092211661
Taiwan	Registration No. 013807
Belarus	Registration no. 7.93447
Canada	Licence 31083 and 72450
Japan	Approval no. 20700BZY00735000
New Zealand	Licence no. 135092
USA	FDA (510k) K040228

1.9 Please complete the table below. If the list price of the technology(s) is not yet known, provide details of the anticipated list price, including the range of possible list prices.

Response

Table A1 Unit costs of technology being appraised

List price (excluding VAT)	***VeriQ 2011***	***VeriQ 2111***	***VeriQ4122***	
	£ 32,000	£ 42,000	£ 47,000	
Average selling price				
Range of selling prices				
Consumables (if applicable) Per consumable: name, list price, average/range selling price, frequency	All CABG procedures will use on average 1.5 – 2 probes depending on the number of grafts and conduit size.			
	PQ Probes	Cardiac sizes 1.5-5mm	50 uses	£1582
	PS Probes	Autoclaveable Cardiac sizes 1.5-7mm	30 uses	£1582
	PA/PB probes	Vascular sizes 6-27mm	50 uses	£1582
Service/maintenance cost and frequency (if applicable)	2 year manufacturers warranty/guarantee. Extended guarantee + service contract £1800 per annum – optional.			
Anticipated life span of technology	10 years			
Average length of use per treatment	Actual measurements take just a minute or so, but the device will be used potentially at different stages so total use time will vary			
Average frequency of use	Daily			
Average cost per treatment	Dependant upon Configuration + avg 1.5 to 2 probes used per procedure:			
	VeriQ 2011	***VeriQ 2111***	***VeriQ4122***	
	£ 99.55	£ 104.09	£ 106.36	

1.10 Would this technology require changes to the way current services are organised or delivered?

Response

No.

1.11 Would other facilities or technologies need to be acquired or used alongside the technology being considered, in order for the claimed benefits to be realised?

Response

No. Ideally, every CABG patient should be included.

1.12 Are there additional tests or investigations needed for selection, or particular administration requirements or a need for monitoring of patients over and above usual clinical practice for this technology?

Response

No.

1.13 What other therapies, if any, are likely to be administered at the same time as the intervention as part of a course of treatment?

Response

None.

1.14 Does the technology require additional infrastructure to be put in place?

Response

No extra infrastructure requirements are required by the technology.

2 Context

2.1 Please provide a brief overview of the disease or condition for which the technology is being considered in the scope.

Response

Coronary Heart Disease Patients who undergo Coronary Artery Bypass Grafts (CABG)

2.2 How many patients are assumed to be eligible for treatment in England and Wales? Present separate results for any groups and subgroups considered in the scope. How are these figures derived? Also present results for the subsequent 5 years.

Response

Around 28,000 CABG operations are performed in the UK each year. There is considerable geographical variation in terms of numbers of operations and referral rates between primary care centres.

http://www.patient.co.uk/doctor/Coronary-Artery-Bypass-Grafting.htm

2.3 Please give details of any relevant NICE guidance or protocols for the condition for which the technology is being used. Specify whether any specific subgroups were addressed.

Response

No NICE guidance has been released on Graft Patency Verification by TTFM.

One piece of guidance was found regarding Intraoperative fluorescence angiography (SPY), but this was more a declaration of safety more than a recommendation of daily use. The guidance states that “There is limited evidence on the diagnostic utility (that is, the extent to which knowledge of its results improves patients’ outcomes) of this procedure”

CABG protocols and some other CHD protocols such as stenting and general CHD prevention were found:

Endoscopic saphenous vein harvest for coronary artery bypass grafting. Interventional Procedure guidance IPG 343. May 2010

Totally endoscopic robotically assisted coronary artery bypass grafting. Interventional Procedure guidance IPG128. June 2005

Intraoperative fluorescence angiography in coronary artery bypass grafting. Interventional Procedure guidance IPG98. October 2004

Off-pump coronary artery bypass grafting. Interventional Procedure guidance IPG35. January 2004

Ischaemic heart disease - coronary artery stents (review). Technology appraisals TA71. October 2003

Drug-eluting stents for the treatment of coronary artery disease. Technology appraisals TA152. July 2008

Stent-graft placement in abdominal aortic aneurysm. Interventional Procedure guidance IPG 163. March 2006

Endovascular stent-graft placement in thoracic aortic aneurysms and dissections. Interventional Procedure guidance IPG127 June 2005

Endovascular stent - grafts for the treatment of abdominal aortic aneurysms. Technology Appraisal TA167. February 2009

Guidance on the prevention of cardiovascular disease at the population level. Public health guidance PH25 June 2010. Expected review date: TBC

2.4 Please present the clinical pathway of care that depicts the context of the proposed use of the technology. Explain how the new technology may change the existing pathway. If a relevant NICE clinical guideline has been published, the response to this question should be consistent with the guideline and any differences should be explained.

Response

The clinical Pathway should not be affected to any great extent as the device is only used for a period of time during the CABG procedure. The technology is used intraoperatively for assessment of flow in new grafts and to verify patency. At present no guidance is issued by NICE for TTFM intraoperative graft patency verification.

2.5 Please describe any issues relating to current clinical practice, including any variations or uncertainty about best practice.

Response

Current clinical practice is varied. Some use a flow measurement device or even an intraoperative imaging device to determine flow in new grafts. The most common form of graft patency verification is clinical assessment, which can include :

- Visual assessment of the anastomosis – looking only at the quality of the graft from the outside doesn't give information about the flow volume or graft quality.
- Digital Palpation – a manual "feel" of the graft to determine pulsatile pressure within the artery. This can also be argued as being lacking in

detail, as even occluded arteries and grafts will have an extent of pulsatile pressure.

The resuts of this are fully dependant on the experience of the surgeon, and do not give any quantative data to compare.

2.6 Please identify the main comparator(s) and justify their selection.

Response

The main comparator is Clinical Assesment as this is most common. There are very few other comparators to VeriQ in the UK market. Most studies and clinical data we have use this as the comparator to TTFM. For this reason it is chosen as the comparator in our cost analyses.

SPY (indocyanine green fluorescence imaging) is the only other comparator in use as we are aware of, but we are unaware of more than one installation across the UK. As this type of imaging gives a picture as opposed to quantative data, we feel that imaging may be more of a complement to TTFM with VeriQ than a direct competitor.

Intraoperative or completion Doppler and Angiogram are rarely heard of, although theoretically simple to carry out, it is not a practice regularly undertaken in the NHS today.

Intraoperative Ultrasound imaging is a viable option, but as with fluorescence imaging, we feel this would be better placed as a complement to TTFM, and MediStim has recently launched a TTFM device with Ultrasound Imaging modality. As this is not covered in the Scope we will not be addressing this at this point.

2.7 Please list therapies that may be prescribed to manage adverse reactions associated with the technology being appraised.

Response

No adverse reactions are related to TTFM with VeriQ

2.8 Please identify the main resource use to the NHS associated with the technology being appraised. Describe the location of care, staff usage, administration costs, monitoring and tests. Provide details of data sources used to inform resource estimates and values.

Response

The Device will be used and operated mainly by Cardiac surgery teams. (Surgeons, OR Nurses) Therefore no extra staff over and above the standard requirements will be needed. The daily running of the device will be easy to administer from within the Cardiac surgery departments and should incur no extra administration or personnel costs.

Extra training costs will be taken by Supplier/manufacturer, and the only cost incurrement is therefore some extra time for the surgical teams to become acquainted with the technology. This will mean a half day of theory, and the rest can be learned in the theatre. We have clinical specialists with over 20 years in the operating theatre as nurses in the cardiac field. As the device is an assessment tool, it has no effect on the surgeons ability to carry out the procedure while learning to use the device. The interpretation of the data and information gathered by the device is quick to learn and the learning curve is steep.

Extra administration costs in the daily running of the machine will be low. The device has a hard disk for data storage and data transfer can be done by USB.

2.9 In addition to technology costs, please consider other significant costs associated with treatment that may be of interest to commissioners (for example, procedure codes and programme budget planning).

Response

There are no other significant costs incurred or related to this technology.

At present there are no DRG or reimbursement codes CABG procedures that include a reimbursement for covering the costs of graft patency evaluation that relies on a technology other than the standard of Clinical Assessment that is most widely used today. Therefore, until such costs are incorporated into CABG reimbursement codes, we will have to look at the potential savings that can be made by using the technology and its potential to prevent a certain number of re-operations on an annual basis.

3 Equity and equality

The National Institute for Health and Clinical Excellence (NICE) is committed to promoting equality and eliminating unlawful discrimination. We aim to comply fully with all legal obligations to:
• promote race and disability equality and equality of opportunity between men and women, and
• eliminate unlawful discrimination on grounds of race, disability, age, sex and gender, sexual orientation, and religion or belief in the way we carry out our functions and in our employment policies and practices.

3.1 Identification of equity and equalities issues

3.1.1 Please specify any issues relating to equality and diversityin NICE guidance, or protocols for the condition for which the technology is being used.

Response

None Highlighted

3.1.2 Are there any equality and diversityissues anticipated for the appraisal of this technology (consider issues relating to current legislation and any issues identified in the scope for the assessment)?

Response

None Highlighted

3.1.3 How have the clinical and economic analyses addressed these issues?

Response

None Highlighted

4 Statement of the decision problem

In this section the decision problem that the submission addresses is specified in the second column, Final scope issued by NICE. This is derived from the final scope issued by NICE and should state the key parameters that the information in the evidence submission will address. The manufacturer or sponsor should specify any additions and/or amendments to the decision problem and rationale in the third and fourth column..

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
Population	Individuals undergoing coronary artery bypass surgery.		
Intervention	Use of VeriQ system during surgery to assess graft flow		
Comparator(s)	Comparators include: clinical assessment of graft flow SPY indocyanine green fluorescence imaging Electromagnetic flow meters Intraoperative or completion Doppler (auscultation) Intraoperative or completion Duplex imaging Intraoperative or completion angiogram	The main comparators are seen to be SPY indocyanine green fluorescence imaging and Clinical assessment, as these are the ones most in use today.	We have very little, if any clinical data comparing VeriQ (TTFM) to any of the other comparators listed here.
Outcomes	Clinical outcome measures include incidence of graft failure, time to graft failure, peri- and post-operative clinical events associated with graft failure (including mortality), frequency of the need for graft revision and changes in VeriQ measurements afterwards as well as the requirement for repeat coronary revascularisation procedures and long term morbidity and mortality. VeriQ may also be helpful in targeting interventions at the end of the surgical procedure if the surgeon is concerned about the immediate results of revascularisation on cardiac function. System-related outcome measures include accuracy of the measurement, time taken to generate and record data during the operation, number of probes used per procedure and number of times each probe can be used.	Additional info: Flow Values of 20 ml/min and with a PI resistance of 5 or less have shown to be key in verifying graft patency. The clinical assessment will address this.	Quote: European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) have recommended graft evaluation before leaving the operating theatre after coronary artery bypass grafting. These guidelines refer to flow < 20mL/min and pulsatility index > 5 as predicting technically inadequate grafts which require revision before leaving the operating theatre.
Cost analysis	The cost analysis should compare the use of the VeriQ system in CABG against the	A de novo cost analysis will be set forward in the	

	most relevant UK comparator which is considered to be clinical assessment of graft flow. The cost analysis should be based on the UK NHS setting. It should comprise NHS costs and personal social services costs (where relevant). Costs should include costs relating to the direct use of the technology such as treatment costs, acquisition cost, running costs and any other health system impact costs. Costs should also include indirect costs, such as infrastructural, maintenance and training costs. The costs associated with complications, adverse events and misdiagnosis relating to the use of the device and the comparator should be considered. Include the time horizon for the accrual of costs and describe the lifetime costs of the technology, where applicable. Sensitivity analysis should be used to address all parameter and model uncertainties associated with the cost analysis.	submission	
Subgroups to be considered	None defined		
Special considerations, including issues related to equity or equality	None defined		

Section B – Clinical effectiveness and cost

5 Clinical evidence

Manufacturers and sponsors are requested to present clinical evidence for their technology in the following section. This section should be read in conjunction with NICE's 'Evaluation Pathway Programme methods guide'. The review of the clinical evidence should be systematic and transparent and a suitable instrument for reporting such as the PRISMA Statement should be used (http://www.prisma-statement.org/statement.htm).

Manufacturers and sponsors are requested to submit the clinical evidence (section 5 and appendices 1-5 (sub-section 7.1-7.5)) in advance of the full submission (for details on timelines, see the NICE document 'Evaluation Pathway Programme process guide' – www.nice.org.uk).

5.1 Identification of studies

5.1.1 Describe the strategies used to retrieve relevant clinical data, both from the published literature and from unpublished data. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. Exact details of the search strategy used should be provided in section 7.2, appendix 2.

Response

Search strategy looked at: Population, intervention and outcomes. Comparing VeriQ with its comparators, both technical comparators and the current practice of Clinical Assessment. We also looked to find how TTFM may or may not give the surgeon a beneficial advantage over other methods.

Studies looking at TTFM which were published before 2004, and whose patient data was collected before2004 were not considered, as VeriQ was released in 2004. Medistim has produced and developed various TTFM based devices over the past 15 years. Studies which refer to non- VeriQ technology

will be omitted due to them not being discussed by the Scope, and that these devices are no longer available on the market. This necessitated a manual search of all initially highlighted studies to find those which were to be excluded on these grounds.

Studies that are written post 2004, with data collection after VeriQ launch, but that do not mention a specific TTFM device, other than naming the manufacturer/supplier will be included.

5.2 Study selection

5.2.1 Describe the inclusion and exclusion selection criteria, language restrictions and the study selection process. A justification should be provided to ensure that the rationale is transparent. A suggested format is provided below.

Table B1 Eligibility criteria used in search strategy

	Clinical effectiveness
Inclusion criteria	Population. Studies of multiple patients included Interventions – CABG Technology – VeriQ or TTFM by MediStim Outcomes – How does VeriQ have benefit/effect on outcome Previously existing Guidance - local or international. Study design – multiple patient studies. Language restrictions – English only included Date – published after 2004 when VeriQ was Launched
Exclusion criteria	Population – case studies of single patients not included Interventions – TTFM in Vascular, Transplant Outcomes – studies where TTFM was used as the “standard” in comparator studies. Technology - Non Medistim TTFM devices (unless as a comparator) and TTFM devices from medistim that predate 2004 Study design – case studies, reviews, and editorials excluded Language restrictions – non English excluded Date – published before VeriQ launch in 2004 Surgical strategy studies – where VeriQ is used as the control when comparing surgical techniques, and is therefore not the subject or comparator in the study

5.2.2 The numbers of studies included and excluded at each stage should be reported

Response

Appendix 7.2.4 describes our full search. This gave us 131 studies. We then used the criteria above in table B1 to manually extract the relevant studies. The full list of included studies is in table B2.

Complete list of relevant studies (RCTs and non-RCTs)

5.2.3 Provide details of **all** studies that compare the intervention with other therapies in the relevant patient group. Highlight which of these studies compare the intervention directly with the appropriate comparator(s) referred to in the decision problem. If there are none, please state this. The list must be complete and will be validated by independent searches conducted by the External Assessment Group. This should be presented in tabular form. A suggested format is presented below.

Table B2 List of relevant studies

Study no. (acronym)	Intervention	Comparator	Population	Primary study ref.
Study 1 Mack et al.	CABG	intraoperative fluorescence imaging, intraoperative angiography, Epicardial achocardiography, TOE, Thermal coronary angio.	1411 grafts 509 patients	Curr Opin Cardiol. 2008 Nov;23(6):568-72
Study 2 Kieser et al.	CABG	Clinical assessment	1015 grafts 336 patients	*Eur J Cardiothorac Surg* 2010;38:155-162
Study 3 Becit et al.	CABG	Clinical Assessment	606 grafts 200 patients	European Journal of Cardio-thoracic Surgery 32 (2007) 313—318
Study 4 Jalal et al.	CABG		553 grafts 186 patients	*Interact CardioVasc Thorac Surg* 2007;6:451-455
Study 5 Nordgaard et al. 2009	CABG	High-frequency epicardial ultrasound	9 grafts 10 pigs	European Journal of Cardio-thoracic Surgery 36 (2009) 137—142
Study 6 Trachiotis et al.	CABG		? grafts ? patients	Eur J Cardiothorac Surg **37** (2010), pp. 1063–1067
Study 7 Nordgaard et al 2011	CABG		grafts patients	Eur J Cardiothorac Surg **39** (2011), p. 431
Study 8 Colli et al.	CABG	Post Operativ Angiografi	grafts patients	*Journal of the American College of Cardiology*, *Volume 54, Issue 24*, *8 December 2009*, *Pages 2337-2338*
Study 9 Leacche et al.	CABG	1. Intraoperative fluorescence imaging (IFI) (SPY; Novadaq Technologies, Inc, Toronto, Canada) 2.High-frequency epicardial ultrasound	grafts patients	Eur J Cardiothorac Surg **37** (2010), pp. 1063–1067
Study 10 Singh et al.	CABG	Indocyanine green (ICG) fluoroscopy (SPY;Novadaq Technologies, Inc, Toronto, Canada)	468 grafts 156 patients	The Journal of Thoracic and Cardiovascular Surgery Volume 139, Issue 2, February 2010, Pages 294-301.e1
Study 11 Kim et al.	CABG		2998 grafts 1481 patients	*J Thorac Cardiovasc Surg* 2010;139:256-262
Study 12 Nordgaard et al. 2010	CABG	Transonic Inc	19 grafts 19 patients	Eur J Cardiothorac Surg. 2010 May;37(5):1063-7. Epub 2009 Dec 23

Study 13 Hatada et al.	CABG	1. Intraoperative fluorescence imaging (IFI) (SPY; Novadaq Technologies, Inc, Toronto, Canada)	10 grafts patients	Gen Thorac Cardiovasc Surg. 2011 Jan;59(1):14-8. Epub 2011 Jan 12.
Study 14 Jokinen et al.	CABG	PCI	204 grafts 75 patients	[European Journal of Cardio-thoracic Surgery (2010) doi:10.1016/j.ejcts.2010.10.006
Study 15 ESC/EACTS guidelines for myocardial revascularisation.	CABG			*EHJ doi:10.1093/eurheartj/ehq277* *Page 33 paragraph 10.2.2*

Response

5.2.4 When studies identified above have been excluded from further discussion, a justification should be provided to ensure that the rationale for doing so is transparent. For example, when studies have been identified but there is no access to the level of study data required, this should be indicated.

Response

The following studies have been excluded from further discussion:

Study no. (acronym)	Intervention	Comparator	Population	Primary study ref.
Study 1 Mack et al.	CABG	intraoperative fluorescence imaging, intraoperative angiography, Epicardial achocardiography, TOE, Thermal coronary angio.	1411 grafts 509 patients	Curr Opin Cardiol. 2008 Nov;23(6):568-72
Study 4 Jalal et al.	CABG		553 grafts 186 patients	*Interact CardioVasc Thorac Surg* 2007;6:451-455
Study 5 Nordgaard et al. 2009	CABG	High-frequency epicardial ultrasound	9 grafts 10 pigs	European Journal of Cardio-thoracic Surgery 36 (2009) 137—142
Study 6 Trachiotis et al.	CABG		? grafts ? patients	Eur J Cardiothorac Surg **37** (2010), pp. 1063–1067
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Study 11 Kim et al.	CABG		2998 grafts 1481 patients	*J Thorac Cardiovasc Surg* 2010;139:256-262
Study 13 Hatada et al.	CABG	1. Intraoperative fluorescence imaging (IFI) (SPY; Novadaq Technologies, Inc, Toronto, Canada)	10 grafts patients	Gen Thorac Cardiovasc Surg. 2011 Jan;59(1):14-8. Epub 2011 Jan 12.

Study 1 ***Mack MJ***

is excluded as it is a review. It makes valid arguments, generally in the area of recommending intraoperative graft assessment. “studies show an immediate graft closure rate of 5–9% and a 1-year closure rate of 20–30% ..... Two methods, transit time flow measurement and intraoperative fluorescence imaging are simple, safe, and expeditious. Intraoperative graft failure detection rates of 2–5% have been reported.

This study fell into our initial criteria, but as it is a review paper we cannot include it from further discussion.

Study 4 ***Jalal***

Is excluded due to lack of correlation between TTFM and graft revision, mortality and MACE.

Study 5 ***Nordgaard et al 2009***
is excluded because it is an assessment which compares competitive flow and stenosis in arterial grafts, and how these affect the flow patterns in the coronary graft, and uses the TTFM and intraoperative ultrasound to quantify and assess this. This does not help us with the decision problem and will not be taken further.

Study 6 ***Trachiotis et al***.
is excluded because it is an editorial letter. Due to its falling into our initial criteria, it was initially included. As it is a clinicians educated opinion it still gives a valid argument, but we felt that we could not include it as it is not a clinical study and will no longer be discussed.

Study 7 ***Nordgaard et al 2011***
is excluded because it is a reply to the above mentioned Study 6. As it too is a clinical opinion based on study outcomes and results, it gives a valid opinion, but again is not set up as a study of patient outcomes. It does however, along with study 6 Trachiotis et al give an insight to the debate within the cardiac field on the intricacies of TTFM and graft patency management. The biggest issue, however is that graft patency is not practiced widely enough on a daily basis, and many surgeons are in agreement of this. For the same reasons as study 6 it will no longer be discussed.

Study 8 ***Colli et al***

is excluded as it too is an editorial letter. The arguments within it are still valid as it cites Becit et al (study 3 in the list above) when it points to TTFM as a cheap, reproducible and reliable form of graft patency verification in comparison to immediate postoperative angiography. It is therefore excluded form further discussion.

Study 9 ***Leacche et al***

is excluded because it is a review paper. It does however give a good review of various itraoperative graft patency technologies and starts off by stating that “graft patency strongly influences early and late outcomes after CABG surgery” it also suggests that until a Hybrid operating suite becomes standard, we must rely on the available reliable technology which is available today for graft patency verification.

Study 10 ***Singh***

Comparative study between TTFM and IFI

Study 11 ***Kim et al***

is excluded due to its collection of data starting before VeriQ was launched. It is however an interesting study, looking at 10 years of data with TTFM. As its data collection is done with older technology than VeriQ we will not be discussing this study any further.

Study 13 ***Hatada et al***

is excluded due to the use of BF 1000 to obtain intraoperative TTFM.

5.3 Summary of methodology of relevant studies

5.3.1 As a minimum, the summary should include information on the study(s) under the subheadings listed in this section. It is expected that all key aspects of methodology will be in the public domain; if a manufacturer or sponsor wishes to submit aspects of the methodology in confidence, prior agreement must be requested from NICE.

Methods

5.3.2 Describe the study(s) design and interventions. Include details of length of follow-up and timing of assessments. The following tables provide a suggested format for when there is more than one study.

Table B3 Comparative summary of methodology of the studies

Study no. (acronym)	**Study 2 Kieser et al.**	**Study 3 Becit et al.**
Location	Calgary,Canada	Erzurum, Turkey
Design	Retrospective observational analysis	Retrospective observsational analysis
Duration of study	April 2004 – april 2007	Not clear: 100 consecutive patients pre feb. 2006 (date of device purchase) 100 consecutive patients after feb. 2006
Method of randomisation (if applicable)	n/a	n/a
Method of blinding (care provider, patient and outcome assessor) (if applicable)	n/a	n/a
Intervention(s) (n =) and comparator(s) (n =)	Cabg: 336 patients, 1015 grafts	200 CABG, 606 grafts 100 patients assessed clinically, 100 patients assessed with TTFM VeriQ
Primary outcomes (including scoring methods and timings of assessments)	Prediction of (MACE) Major adverse cardiac events	Morbidity, peri/post op infarctions and mortality rates dropped with use of TTFM and inreaoperative graft revision.
Secondary outcomes (including scoring methods and timings of assessments)	Interpretation of data and values shown by VeriQ TTFM which led to a decision to assess and revise grafts Intraopertaively	
Duration of follow-up	6-8 weeks post-op	n/a

Study no. (acronym)	**Study 12 Nordgaard et al 2010**
Location	Trondheim, Norway
Design	Direct Comparative assessment of similar technologies
Duration of study	unknown
Method of randomisation (if applicable)	n/a
Method of blinding (care provider, patient and outcome assessor) (if applicable)	n/a
Intervention(s) (n =) and comparator(s) (n =)	CABG – 19 patients Transonic. 19 patients
Primary outcomes (including scoring methods and timings of assessments)	VeriQ shows a higher Pulsatility index (PI) to Transonic systems
Secondary outcomes (including scoring methods and timings of assessments)	A lower PI may show the graft to better than it is.
Duration of follow-up	

Study no. (acronym)	**Study 14 Jokinen et al**
Location	Helsinki, Finland
Design	Prospective analysis
Duration of study	
Method of randomisation (if applicable)	
Method of blinding (care provider, patient and outcome assessor) (if applicable)	
Intervention(s) (n =) and comparator(s) (n =)	GABG - 204 grafts
Primary outcomes (including scoring methods and timings of assessments)	TTFM detects Graft failure within 6 months of CABG
Secondary outcomes (including scoring methods and timings of assessments)	
Duration of follow-up	199 days

Participants

5.3.3 Provide details of the eligibility criteria (inclusion and exclusion) for the study. The following table provides a suggested format for the eligibility criteria for when there is more than one study. Highlight any differences between the studies.

Due to the nature of the Device, it has no factors in its use, design or features that would exclude any patients from its use intraoperatively. This is therefore not a factor in any of the studies we have discovered or highlighted and is not applicable here. None of the studies refer to exclusion factors or excluded patients. All patients who undergo CABG are eligible for inclusion in studies.

Table B4 Eligibility criteria in the studies

Study no. (acronym)	Inclusion criteria	Exclusion criteria
Study 1	Typical inclusion criteria may relate to age, gender and clinical diagnosis	Typical exclusion criteria may relate to participant safety
Study 2		
Etc.		
Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee		

5.3.4 Describe the patient characteristics at baseline. Highlight any differences between study groups.

Patients included are always CABG patients.

There are no differences in the patient groups for each study, as the studies are mainly retrospective observational studies. Some studies highlight diabetes patients, age and sex. But these criteria are not inclusion, exclusion or differentiating factors for the different groups within the study data.

Outcomes

5.3.5 Provide details of the outcomes investigated and the measures used to assess those outcomes. Indicate which outcomes were specified in the study protocol as primary or secondary, and

whether they are relevant with reference to the decision problem. Data provided should be from pre-specified outcomes rather than post-hoc analyses. When appropriate, also provide evidence of reliability or validity, and current status of the measure (such as use within UK clinical practice). The following table provides a suggested format for presenting primary and secondary outcomes when there is more than one study.

Table B5 Primary and secondary outcomes of the studies

Study no. (acronym)	Primary outcome(s) and measures	Reliability/validity/ current use in clinical practice	Secondary outcome(s) and measures	Reliability/validity/ current use in clinical practice
Study 2 Kieser et al.	The objective of the study was to assess the value of the TTF method in predicting postoperative major adverse cardiac events (MACE)	The use of TTF in assessing graft patency is recommended in the ESC/EACTS Guidelines	Logistic regression analysis predicting MACE using TTF and baseline measurements	
Study 3 Becit et al.	The purpose of the study was to evaluate the effect of detection of graft dysfunction by intraoperative TTFM on the surgical results of on-pump CABG. Effects were measured through morbidity, peri/post op infarctions and mortality.			
Study 12 Nordgaard et al. 2009	The aim is to assess the potential variability of the PI as calculated by MediStim and Transonic flowmeters			
Study 14 Jokinen et al.	Predictive values of TTFM in CABG with regard to short-term graft patency and long-term patient survival.	The use of TTF in assessing graft patency is recommended in the ESC/EACTS Guidelines		

Statistical analysis and definition of study groups

5.3.6 State the primary hypothesis or hypotheses under consideration and the statistical analysis used for testing hypotheses. Provide details of the power of the study and a description of sample size calculation, including rationale and assumptions. Provide details of how the analysis took account of patients who withdrew. The

following table provides a suggested format for presenting the statistical analyses in the studies when there is more than one study.

Table B6 Summary of statistical analyses in studies

Study no. (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
Study 2 Kieser et al	In the present study, we used TTF in 336 consecutive patients to assess the value of this method in predicting postoperative major adverse cardiac events (MACEs). Our findings suggest that the pulsatility index (PI), one of three TTF measurements, is highly predictive of outcomes.	Continuous variables are expressed using the median and interquartile range since the distributions were highly skewed. Exact binomial 95% confidence intervals (CIs) were calculated for proportions. The data of two independent groups were compared by Fisher's exact test (FET). Initially, a univariate logistic regression analysis was done for each of the potential predictor variables of MACE. Variables that were significant at $p < 0.10$ were also included in a multivariate regression model. Statistical analyses were performed using Stata.8.0 (StataCorp, College Station, TX, USA). A p value of <0.05 was considered to be statistically significant.	336 patients, 1015 grafts	
Study 3 Becit et al	The purpose of this study is to evaluate the effect of detection of graft dysfunction by intraoperative transit time flow measurement (TTFM) on the surgical results of on-pump coronary artery bypass grafting. TTFM seems to be a crucial tool for deciding if a graft is well-functioning or not, and it allows for improvement of graft failure during operation. Our results suggest that detection of graft dysfunction intraoperatively by TTFM improves the surgical outcome.	All data were expressed as means _ standard deviation. Comparison of data between the two groups was performed using the independent two-sample t-test, the independent two-ratio test (z test) and the independent Fisher's chi-squared test. A p value of less than 0.05 was considered to be statistically significant.	200 patients, 606 grafts	
Study 12 Nordgaard et al. 2010	The aim was to compare pulsatility index (PI) values recorded by the MediStim and Transonic flowmeters in two different clinical settings: (1) analysis of the flow patterns recorded simultaneously by both flowmeters in the same CABGs; and (2) evaluation of flow patterns under different levels of filter settings in the same grafts.	The grafts were nested into LIMA-LAD, single and double sequential SVGs to the left and right coronary arteries, respectively. In Table 1, a logarithmic transformation of the flow data was performed to achieve normal distribution. The comparisons between grafts from the two cardiac centres were performed using two sample ttests except for the single SVGs to the left coronary artery, where a random effects model with random intercept using the 'xtreg' command in STATA was used. A random effects model was used to account for repeated	10 patients, 19 grafts	

		measurements as several patients got more than one single SVG to the left coronary artery system. A Wilcoxon signed rank test was used to compare the simultaneous flow assessments in the same grafts. Bland—Altman plots of the simultaneous flow measurements were made in Excel. The PI values are expressed as geometric mean and 95% confidence interval. $p < 0.05$ was considered significant. Statistical analysis was performed using SPSS for Windows version 15 (SPSS Inc., Chicago, IL, USA) and STATA for Windows version 10 (StataCorp, College Station, TX, USA).		
Study 14 Jokinen et al.	A considerable number of coronary artery bypass grafts (CABGs) fail either immediately or soon after surgery. Early graft failure is inevitably associated with serious clinical implications: myocardial ischemia or infarction, and thus potentially compromises the long-term outcome of the patients TTFM predicts graft failure within the 6 months after CABG. At present, transit-time flow measurement (TTFM) is the most common intra-operative method for assessment of the function of the graft. TTFM is convenient, and the measurement results are sufficiently valid, exact, and reproducible for clinical purposes.	Altogether,75 CABG operated patients served as subjects, consisting of the sample size of 204 consecutively measured grafts. Qualitative data are expressed as frequencies and percentages. Normally distributed quantitative data are expressed as mean ± standard deviations and skewed data are presented as median with its interquartile range (IQR, 1st quartile—3rd quartile),as appropriate, and analyzed using the non-parametric Mann—Whitney U-test. Late survival was assessed by Kaplan—Meier's survival analysis, and the log-rank test was used to determine the difference in mortality. Receiver operating characteristic (ROC) curves of sensitivity and specificity were used to assess particular cut-off values for the flow parameters with regard to graft patency. Spearman's rank correlation test was used and the appropriate correlation coefficient was calculated to describe the correlation between the measured flow values and graft patency. Differences with a p value <0.05 were considered statistically significant, and all tests were two sided. The Statistical Package for Social Sciences (SPSS) version 15.0 was used for the statistical calculations (SPSS Inc, Chicago, IL, USA).	75 patients, 204 grafts	

5.3.7 Provide details of any subgroup analyses that were undertaken and specify the rationale and whether they were pre-planned or post-hoc.

Response

None taken

Participant flow

Where applicable, provide details of the numbers of patients who were eligible to enter the study(s), randomised, and allocated to each treatment. Provide details of, and the rationale for, patients who were lost to follow-up or withdrew from the study.

Response

All CABG patients who were included in the studies were eligible by definition of being CABG patients. As the device is used intraoperatively, and not over an extended period of time, it will be difficult for patients to drop out or be excluded from the study data.

5.4 Critical appraisal of relevant studies

5.4.1 The validity of the results of an individual study will depend on the robustness of its overall design and execution, and its relevance to the decision problem. Each study that meets the criteria for inclusion should therefore be critically appraised. Whenever possible, the criteria for assessing published studies should also be used to assess the validity of unpublished and part-published studies. The critical appraisal will be validated by the External Assessment Group.

5.4.2 Please provide as an appendix a complete quality assessment for each study. See section 7.3, appendix 3 for a suggested format. For the quality assessments use an appropriate and validated quality assessment instrument. Key aspects of quality to be considered can be found in ‘Systematic reviews: CRD’s guidance for undertaking reviews in health care’ (www.york.ac.uk/inst/crd).

5.5 Results of the relevant studies

5.5.1 Provide the results for all relevant outcome measure(s) pertinent to the decision problem. Data from intention-to-treat analyses should be presented whenever possible and a definition of the included patients provided. If patients have been excluded from the analysis, the rationale for this should be given. If there is more than one study, tabulate the responses.

5.5.2 For each outcome for each included study, the following information should be provided.

- The unit of measurement.
- The size of the effect; for dichotomous outcomes, the results ideally should be expressed as both relative risks (or odds ratios) and risk (or rate) differences. For time-to-event analysis, the hazard ratio is an equivalent statistic. Both absolute and relative data should be presented.
- A 95% confidence interval.
- Number of participants in each group included in each analysis and whether the analysis was by ‘intention to treat’. State the results in absolute numbers when feasible.
- When interim study data are quoted, this should be clearly stated, along with the point at which data were taken and the time remaining until completion of that study. Analytical adjustments should be described to cater for the interim nature of the data.

Other relevant data that may assist in interpretation of the results may be included, such as adherence to medication and/or study protocol.

- Discuss and justify definitions of any clinically important differences.
- Report any other analyses performed, including subgroup analysis and adjusted analyses, indicating those pre-specified and those exploratory.

Response

Study 02, Kieser et al.

In this study, 1000 grafts on 336 patients were followed up for an average of 3 years. The results of the analysis of the main objective ih the Kieser et al. publication are presented in the two tables below. The findings are that a PI value > 5 is a predictor both for the occurrence of future MACE and mortality, while flow and diastolic filling do not show such results. PI > 5 as a predictor is also seen in the multivariate logistic analysis together with age and admission type.

The authors' conclusions are that "The PI, obtained by TTF measurement, is a valuable tool to assess adequacy of arterial grafts and predict outcomes. Postoperative adverse events, especially operative mortality, are significantly higher in patients with grafts with a high PI. Such grafts should be carefully assessed even when there is no other indicator of a suboptimal graft function clinically, by either EKG or echocardiography. The authors suggest that intra-operative use of TTF measurement of arterial aortocoronary bypass grafts should become the standard of care."Study 2: Kieser et al.

Relations between TTF and MACE

	MACE			Mortality			Deaths excluding 32 emergency patients		
	Patients (N)	%	p-value	Patients (N)	%	p-value	Patients (N)	%	p-value
PI									
> 5	10/59	17%	0.005	7/59	12%	0.011	5/54	9%	0.020
≤ 5	15/277	5%		9/277	3%		5/250	2%	
Flow									
< 15	8/73	11%	0.209	4/73	5%	0.757	3/69	4%	0.700
≥ 15	17/263	6%		12/263	5%		7/235	3%	
DF[a]									
< 45	6/43	6%	0.124	4/43	9%	0.256	4/40	10%	0.043
≥ 45	18/263	14%		12/263	5%		6/234	3%	

Flow (cc min^{-1}), PI, pulsatility index; DF, diastolic filling.

[a] DF recorded in 306/336 patients (91%) (DF is dependent on the EKG trace, which was not always acceptable.)

Study 2 Kieser et al.
Multivariate logistic regression predicting MACE

Variable	Odds ratio	95% CI	p value
PI > 5	4.23	1.69, 10.59	0.002
Age (per 10 years)	1.67	1.08, 2.57	0.022
Admission			
Out-patient	1.00		
In-patient	4.61	1.28, 16.58	0.019
Emergent	15.29	3.52, 66.37	<0.001

Study 03 Becit et al.

The main results of the study are presented in the table below. Group A is the control group, consisting of the last 100 consecutive patients treated before the TTFM system was acquired and group B consist of the first 100 patients treated after acquiring the TTFM system. The study shows that there was a statistically significant reduction in the rate of overall morbidity, IABP insertion, peri-or postoperative infarction and overall mortality. The authors conclude that “we strongly believe that a meticulous operative technique should be supported with intraoperative TTFM in completed bypass grafts. Because our results suggest that detection of graft dysfunction intraoperatively by TTFM improves the surgical results.”

Study 3: Becit et al.
Complication and mortality rate

Parameters	Group A (n=100)	Group B (n=100)	p value
Overall morbidity (n)	16	6	<0.05
Re-exploration for bleeding	3	3	>0.05
Deep sterna infection	1	1	>0.05
IABP insertion	7	1	<0.05
Peri- or postoperative infarction	5	-	<0.05
Overall mortality (n)	4	-	<0.05

IABP = intra aortic balloon punp

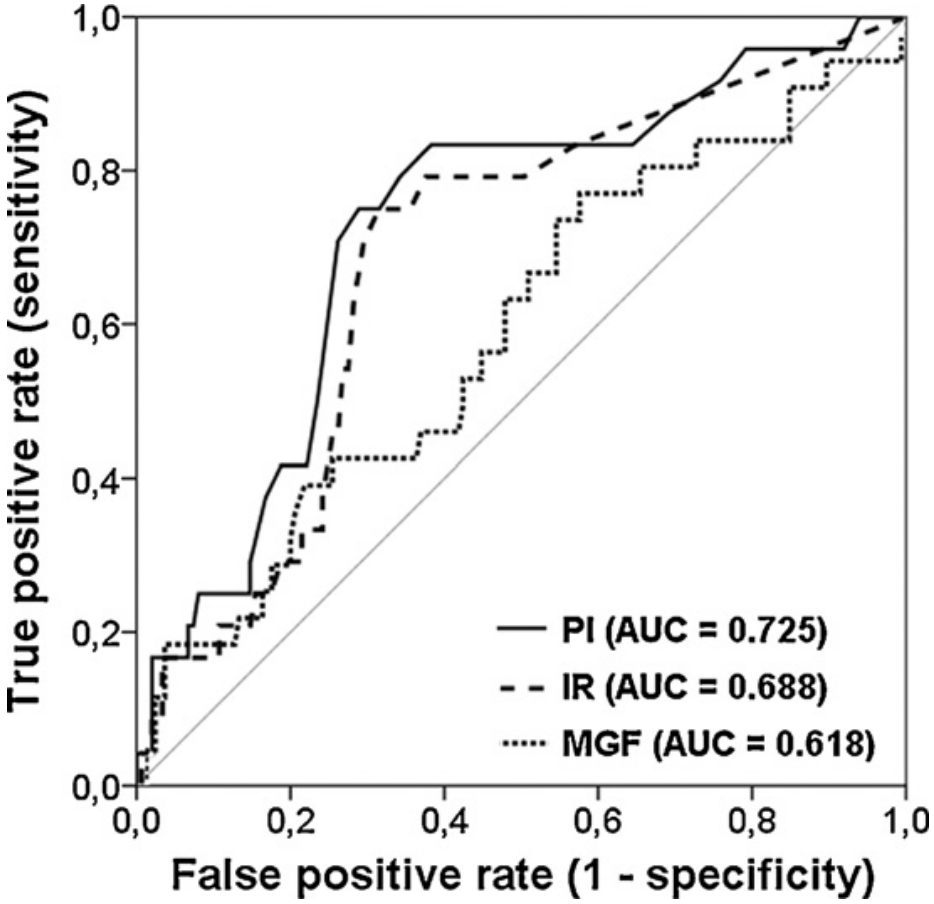
Study 12: Nordgaard et al. 2009

The study showed that the MediStim and Transonic flowmeter provided mean PI and standard deviations of 2.7 ± 1.2 and 1.8 ± 0.6, respectively ($p < 0.001$; Wilcoxon signed ranks test). The authors conclude that "MediStim and Transonic TTFMs are not directly comparable because of their filter settings at 20 and 10 Hz, respectively. Different levels of filter settings in the flowmeters determine different shapes in the flow curves, which results in different PI values. In particular, more pronounced differences in PIs were noted when the PI was around 3. Thus, the type of flowmeter should always be reported together with the graft flows and PI."

Study 14: Jokinen et al.

It is unclear whether this study was done using the VeriQ system. It is stated in the publication that the VeriQ system was used, but it is also stated that the patients were included between March 2001 and December 2002, a time it is believed that the VeriQ system was not operative or approved for use. The results of the study is included in the relevant pool of literature and presented here, since it is stated that the VeriQ system was used.

In this study 75 patients were followed up for 8.4 years on average. The figure below presents the receiver operating characteristic (ROC) corves representing the accuracy of the pulsatility index (PI), insufficiency ratio (IR) and mean graft flow volume (MGF) for predicting complete graft occlusion after CABG. Occlusions were determined by coronary angiography within 199 ± 42 days after CABG. AUC: Area under the curve.



The mean PI values for the completely occluded grafts was 3.3 and for patent graft 2.2 with a p-value of 0.003. The corresponding values for MGF and IR are 38 ml/min, 45 ml/min, P=not significant, and 1.6, 0.2, p=0.03.

No data was given for morbidity and mortality, but it was stated that TTFM variables did not “correlate with clinically relevant postoperative end points (myocardial infarction, stroke, or death).”

The authors conclude that “TTFM predicts graft failures within 6 months after CABG, but does not predict long-term outcome.”

Comments:

The three studies presented differ substantially in size, from 75 to 200 and 336 patients. Kieser et al. did mostly not act on the TTFM information alone for graft revision, while Becit et al. acted on abnormal values after checking twisting, kinking, air bubbles or spasms. Jokinen et al. shows that there PI predicts graft patency, Kieser et al. shows that PI predicts 3-year mortality and

morbidity and Becit shows that acting on the predictions of PI reduces the mortality and morbidity significantly in the group being assessed with TTFM.

5.6 Meta-analysis and evidence synthesis

When considered appropriate, techniques for evidence synthesis such as meta-analysis, and indirect and mixed treatment comparisons can be used.

5.6.1 Describe the technique used for meta-analysis and/or evidence synthesis, the steps undertaken and results of the analysis including methodology. For example, when direct comparative evidence is not available, indirect treatment comparison methods can be used. The following descriptions should be included if indirect or mixed treatment comparisons are undertaken.

- Identification, selection, methodology and quality assessment of relevant studies
- Summary of the studies used to conduct the indirect comparison. For the selected studies, provide a summary of the data used in the analysis.
- Indirect/mixed treatment comparison methodology.
- Results of the analysis.
- The statistical assessment of heterogeneity and any sensitivity analyses

Response

No Meta Analysis has been conducted to date.

5.6.2 If evidence synthesis is not considered appropriate, a rationale should be given and a qualitative overview provided. The overview should summarise the overall results of the individual studies with reference to their critical appraisal.

Response

VeriQ has been shown to predict immediate to short term patency in CABG. We will express below the studies which show a strong advantage of using TTFM over clinical assessment and how it affects outcomes.

Reference	Comparator	Advantage identified	Result
Study 2 – Kieser et al	Clinical assessment	VeriQ TTFM gives a PI value which is a valuable tool in assessing adequacy of arterial grafts to predict outcomes	Patients with high PI values (over 5) are 4 times more likely to suffer MACE.
Study 3 Becit et al	Clinical assessment	VeriQ TTFM gives opportunity to review poor grafts intraoperatively.	Morbidity dropped from 16 to 6% Peri and post op infarction rates dropped from 5% to 0% and mortality rates dropped from 4% to 0%
Study 14 Jokinen et al	PCI		TTFM predicts graft failure within 6 months of CABG

5.7 Adverse events

This section should provide information on the adverse events experienced with the technology in relation to the decision problem. For example, post-marketing surveillance data may demonstrate that the technology shows a relative lack of adverse events commonly associated with the comparator, or the occurrence of adverse events is not significantly associated with other treatments.

5.7.1 If any of the main studies are designed primarily to assess safety outcomes, please repeat the instructions specified in sections 5.1 to 5.5 for the identification, selection, methodology and quality of the studies, and the presentation of results. Examples for search strategies for specific adverse effects and/or generic adverse-effect terms and key aspects of quality criteria for adverse-effects data can found in 'Systematic reviews: CRD's guidance for undertaking reviews in health care' (www.york.ac.uk/inst/crd). Exact details of the search strategy used and a complete quality assessment for each study should be provided in sections 7.4 and 7.5, appendices 4 and 5.

Response

5.7.2 Please provide details of all important adverse events. For each group, give the number with the adverse event, the number in the group and the percentage with the event. Then present the relative risk and risk difference and associated 95% confidence intervals for each adverse event. A suggested format is shown below.

No adverse events are recorded with the device. The device is certified for direct cardiac use and is for use only by a surgeon, who in turn must be trained to use the device.

Table B7 Adverse events across patient groups

System organ/ class/adverse events	**Time period 1**			**Time period 2 etc.**		
	Intervention % of patients (n = x)	**Comparator % of patients (n = x)**	**Relative risk (95% CI)**	**Intervention % of patients (n = x)**	**Comparator % of patients (n = x)**	**Relative risk (95% CI)**
Class 1 (for example, nervous system disorders)						
Adverse event 1						
Adverse event 2						
Class 2 (for example, vascular disorders)						
Adverse event 3						
Adverse event 4						
CI, confidence interval Adapted from European Public Assessment Reports published by the European Medicines Agency						

5.7.3 Give a brief overview of the safety of the technology in relation to the decision problem.

Response

The technology has been available on the market in various forms for over 15 years. It considered to be very safe and presents no threat to users or patients. No protective equipment is required for its use.

5.8 Interpretation of clinical evidence

5.8.1 Please provide a statement of principal findings from the clinical evidence highlighting the clinical benefit and harms from the technology.

Response

The primary findings are:

- TTFM is safe and gives a quantative assessment of graft patency allowing faulty or less than optimal grafts to be revised. – Becit et al
- TTFM gives a PI (pulsatile index) which is a reliable predictor of MACE – Kieser et al
- Mortality rates have been seen to be reduced after revising grafts intraoperatively based on TTFM findings – Becit et al
- Performing TTFM with VeriQ on every patient is the only way to ensure a consistent result. - ESC/EACTS guidelines for Myocardial revascularisation
- A defined set of paramaters can be used to identify potentially non-patent grafts. - Kieser et al
- TTFM with VeriQ can predict Graft failure within 6 months of CABG – Jokinen et al.

5.8.2 Please provide a summary of the strengths and limitations of the clinical-evidence base of the intervention.

Response

The main strength of the clinical evidence supporting VeriQ is that none of the sdudies performed have been paid for by MediStim, many studies have been published in which MediStim has been totally unaware that VeriQ has been

used in the study, making it totally independent data. In some cases MediStim has provided support in the way of devices on loan to those performing the study.

Some of the studies included have a small patient base, this could be improved and a larger patient group could be preferable.

5.8.3 Please provide a brief statement of the relevance of the evidence base to the decision problem. Include a discussion of the relevance of the outcomes assessed in clinical studies to the clinical benefits experienced by patients in practice.

Response

The decision problem looks at the comparison of VeriQ over clinical assessment, and whether the Surgeon using VeriQ is therefore better equipped to improve his or her patients outcomes. A reduction in early mortality, early graft failure and reoperation rates will indicate this.

The studies included look at post operative outcomes, adverse events, and how the use of VeriQ either can predict these or be used as reason for ungergoing an intraoperative revision of Grafts. They compare VeriQ to Clinical assessment and other available technologies.

The general opinion is that intraoperative assessment of Grafts is an important part of CABG, as CABG is one of few cardiological procedures that doesn’t routinely recieve any verification. TTFM is identified as being predictable, reliable, cost effective and readily available as a verification method, other than clinical assessment.

5.8.4 Identify any factors that may influence the external validity of study results to patients in routine clinical practice; for example, how the technology was used in the study, issues relating to the conduct of the study compared with clinical practice, or the choice of eligible patients. State any criteria that would be used in clinical practice to

select patients for whom treatment would be suitable based on the evidence submitted.

Response

Studies' patient groups fall mainly into 2 categories:

- Those that directly compare TTFM to another technology or clinical assessment, and therefore have 2 patient groups
- Those that use the same patient group and compare VeriQ with another technology to compare data.

Due to the nature of VeriQ and its (diagnostic) non therapeutic action, the only way a true comparison can be done is if all patients during a set time period are submitted to TTFM measuring during their CABG, and the results then measured against a comparator or present clinical practice. The Device is used during a short period of time during a CABG procedure, and does not greatly affect the length of a CABG procedure. Neither does it have a great impact on the routines within a CABG, other than allowing a Surgeon to revise and attempt to improve the flow of any grafts that may appear to be sub-optimal.

6 Analysis of Cost

6.1 Published cost-effectiveness and cost evaluations

Identification of studies

6.1.1 Describe the strategies used to retrieve relevant health economics studies from the published literature and identify all unpublished data. Health economics studies should include all types of economic evaluation and cost studies, including cost analyses and budget impact analyses. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. The search strategy used should be provided as in section 7.6, appendix 6.

In order to retrieve relevant health economic papers a list of relevant search terms was prepared. The search terms were decided upon on the basis of retrieving economic evaluations and costs studies for the medical device in question and the relevant surgery for which the device is applied. The search strategy was expected to both limit the search results and provide the relevant literature for the treatment in question.

The search terms were consistently used in all relevant search engines, i.e. the terms and the order of the terms was the same. The following search terms and structure were used:

1. coronary artery bypass
2. coronary artery graft
3. cabg
4. transit time
5. transit-time
6. ttf
7. ttfm
8. economic
9. cost
10. #1 or #2 or #3
11. #4 or #5 or #6 or #7
12. #8 or #9
13. #10 and #11 and #12

To retrieve relevant health economics papers, a search were performed on the 17th of March 2011 using the service provider OvidSP. OvidSP comprise more than hundred databases, among them Embase, Econlit, EBM Reviews, Medline ® and Medline ® In-Process. In addition, a literature search was performed on the 23rd of March 2011 using a selection of databases provided by Proquest Dialog Datastar. The selection of databases were the following; Cochrane, Lancet Titles, Cochrane, Allied & Complementary Medicine™,British Library Inside Conferences, DH-DATA: Health Administration, Medical Toxicology & Environmental Health, ERIC, ESPICOM Pharmaceutical & Medical Device News, Gale Group Health Periodicals Database, Gale Group PROMT®, International Pharmaceutical Abstracts, MEDLINE® and Polymer Library. A literature search was also conducted on the 17th of March in the NHS EED database.

One of two search limitation was that relevant literature had to refer to the search terms in the title and/or the abstract. If search terms only were referred to in the text and not the title and/or abstract it was expected to provide irrelevant search results. In addition, the search in Proquest Dialog Datastar was limited to scientific journals. No limitation in terms of publication date range was used.

Response

Description of identified studies

6.1.2 Provide a brief overview of each study, stating the aims, methods, results and relevance to decision-making in England and Wales. Each study's results should be interpreted in light of a critical appraisal of its methodology. When studies have been identified and not included, justification for this should be provided. If more than one study is identified, please present in a table as suggested below.

The literature search provided citations for two published articles:

1. Mujanović E, Kabil E, Bergsland J.Transit time flowmetry in coronary surgery--an important tool in graft verification. Bosn J Basic Med Sci. 2007 Aug;7(3):275-8.
2. Mujanović E, Bergsland J, Hadziselimović M, Softić M, Azabagić A. Intraoperative quality control in the coronary artery bypass grafting]. [Article in Bosnian] Med Arh. 2006;60(6):351-5.

None of the identified studies is regarded as relevant. The sections below present the rationale for disregarding the identified studies.

Study number 1 was not available for purchase from the Bosnian Journal of Basic Medical Sciences, and only available as abstract. Although the study analyzed TTFM experience in CABG operations, it was not an economic evaluation of TTFM. The search term *cost* which appeared in the abstract (along with TTFM and CABG), referred to CABG surgery without the use of cardiopulmonary bypass, being a preferential surgical method because of significant *cost* savings.

Study number 2, was written in Bosnian, with only the abstract being available in English. In the conclusion of the abstract it was stated that TTFM would improve the operative results and the cost-effectiveness of CABG. We contacted Dr. Jacob Bergsland, one of the authors of this article.
Dr. Bergsland stated that the study was not an economic evaluation of TTFM. The statement on cost-efficiency was according to Dr. Bergsland to be regarded as an assumption made by himself and the co-authors based on their experience with TTFM, rather than an assertion based on economic analyses.

Table B8 Summary list of all evaluations involving costs

Study	Year	Country(ies) where study was performed	Summary of model	Patient population (average age in years)	Costs (currency) (intervention, comparator)	QALYs (intervention, comparator) (when referred to in the study)	ICER (per QALY gained) (if applicable)
Study 1							
Study 2							
Etc.							
ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life year(s)							

6.1.3 Please provide a complete quality assessment for each health economics study identified. Use an appropriate and validated instrument, such as those of Drummond and Jefferson (1996)[1] or Philips et al. (2004)[2]. For a suggested format based on Drummond and Jefferson (1996), please see section 7.7, appendix 7.

Response

Not Applicable, no relevant studies were identified

6.2 De novo cost analysis

6.2.1 Please provide the rationale for undertaking further cost analysis in relation to the decision-problem.

Response

No existing cost analyses were found during the search conducted. Since the TTFM technology adds costs to the CABG, it is necessary to study potential cost savings as well.

[1] Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83.

[2] Philips Z, Ginnelly L, Sculpher M, et al. (2004) Quality assessment in decision-analytic models: a suggested checklist (Appendix 3). In: Review of guidelines for good practice in decision-analytic modelling in health technology assessment. Health Technology Assessment 8: 36.

Patients

6.2.2 What patient group(s) is(are) included in the cost analysis?

Response

The literature providing input data consist of consecutive patients undergoing CABG. Hence, the population being studied comprises coronary heart disease patients undergoing CABG. In the Becit 2007 study, all CABG were done on-pump, while the Kieser 2010 study comprises both on- and off-pump CABG.

Model structure

6.2.3 Please provide a diagrammatical representation of the model you have chosen.

Response

The cost analysis calculates mean costs for a patient using rates of occurrence and mean unit costs per defined event, for CABG with and without TTFM. Overall costs for each arm in the analysis are not calculated for all resource use, only for the resource use where there may be differences between the arms, i.e. the incremental cost.

6.2.4 Please justify the chosen structure in line with the clinical pathway of care identified in section 2.4.

Response

The clinical Pathway should not be affected to any great extent, except for an expected decrease in the occurrence of MACE. In addition to reducing the rate of such events, this would affect the total resource use per patient over time.

6.2.5 Please define what the health states in the model are meant to capture.

Response

The economic analysis presented here is not based on health states except through the kind of events reported in the literature that when their rates of occurrence is changed, would affect the total costs.

6.2.6 How does the model structure capture the main aspects of the condition for patients and clinicians as identified in section 2 (Context)? What was the underlying disease progression implemented in the model? Or what treatment was assumed to reflect underlying disease progression? Please cross-reference to section 2.1.

Response

The model considers all coronary heart disease patients who undergo CABG either with or without TTFM.

6.2.7 Please provide a table containing the following information and any additional features of the model not previously reported. A suggested format is presented below.

Table B9 Key features of analysis

Factor	Chosen values	Justification	Reference
Time horizon	Not specified, but within 1-3 years after CABG	Data only exist from 2 publications. One does not specify the observational period	Becit 2007, Kieser 2010
Cycle length	Only one cycle is used.		
Half-cycle correction			
Discount of 3.5% for costs	No discount rate is used. The time for when events occur is not expressed in detail in the literature		
Perspective (NHS/PSS)	NHS	NHS costs are used	
NHS, National Health Service; PSS, Personal Social Services.			

Technology

6.2.8 Are the intervention and comparator(s) implemented in the model as per their CE marking as stated in sections 1.3 and 1.5? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specified decision problem?

Response

Yes

6.2.9 Please note that the following question refers to clinical continuation rules and not patient access schemes. Has a treatment continuation rule been assumed? If the rule is not stated in the (draft) IFU, this should be presented as a separate scenario by considering it as an additional treatment strategy alongside the base-case interventions and comparators. Consideration should be given to the following.

- The costs and health consequences of factors as a result of implementing the continuation rule (for example, any additional monitoring required).
- The robustness and plausibility of the endpoint on which the rule is based.
- Whether the 'response' criteria defined in the rule can be reasonably achieved.
- The appropriateness and robustness of the time at which response is measured.
- Whether the rule can be incorporated into routine clinical practice.
- Whether the rule is likely to predict those patients for whom the technology is particularly cost effective.
- Issues with respect to withdrawal of treatment from non-responders and other equity considerations.

Response

The model considers only those coronary heart disease patients who will undergo CABG. The analysis provides costs for an average patient; no selection of patients is done.

6.3 Clinical parameters and variables

When relevant, answers to the following questions should be derived from, and be consistent with, the clinical-evidence section of the submission (section 5). Cross-references should be provided. If alternative sources of evidence have been used, the method of identification, selection and synthesis should be provided as well as a justification for the approach.

6.3.1 Please demonstrate how the clinical data were implemented into the model.

Response

Survival outcome is not included in the cost analysis. Cost-effectiveness is not part of this analysis due to the scarcity of available data. Morbidities following CABG are included through the resource use needed to treat the conditions.

Only clinical data that show statistically significant differences in morbidities between CABG surgery with and without TTFM are considered in the model.

6.3.2 Demonstrate how the transition probabilities were calculated from the clinical data. If appropriate, provide the transition matrix, details of the transformation of clinical outcomes or other details here.

Response

Transition probabilities are not used in this model, since the time aspect is not included. Rates of occurrence are used to weigh the cost of treating MACE and other events according to frequency.

6.3.3 Is there evidence that (transition) probabilities should vary over time for the condition or disease? If so, has this been included in

the evaluation? If there is evidence that this is the case, but it has not been included, provide an explanation of why it has been excluded.

Response

Not applicable in the approach taken.

6.3.4 Were intermediate outcome measures linked to final outcomes (for example, was a change in a surrogate outcome linked to a final clinical outcome)? If so, how was this relationship estimated, what sources of evidence were used, and what other evidence is there to support it?

Response

No intermediate outcome measure is used.

6.3.5 If clinical experts assessed the applicability of values available, or estimated or adjusted any values, please provide the following details[3]:

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical speciality whose opinion was sought
- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method(s) used to collect and collate the opinions.

The uncertainty around these values should be addressed in the sensitivity analysis.

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[3] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

Response

Clinical expertise has been consulted regarding time spent on using the TTFM technique. Dr. Kieser was consulted for her extensive knowledge and experience in the use of TTFM. She is the primary author of Kieser 2010, a publication presenting the results of more than 1000 grafts in 336 patients. Dr. Bergsland has also been consulted due to his long experience with TTFM and his proximity to the authors of this document. He is Norwegian practicing at the National Hospital in Oslo. The authors of this document also have their working place in Oslo.

Summary of selected values

6.3.6 Please provide a list of all variables included in the cost analysis, detailing the values used, range (distribution) and source. Provide cross-references to other parts of the submission. Please present in a table, as suggested below.

Table B10 Summary of variables applied in the economic model

Costs	Value used	Value 1	Value 2	Value 3	Value 4	Value 5	Source
VeriQ cost per probe used in same procedure, £	58,56	58,56	61,23	62,56			Manufacturer Submission document for systems VeriQ 2011, VeriQ2111 and VeriQ 4122, resp, Table A1
EB10Z: Actual or Suspected Myocardial Infarction, £	1415,20	1415,20					
VC38Z: Rehab for acute MI and other cardiac disorders, £	251,76	251,76					
PA17B: Deep sternal infection,	860,55	860,55	687,54	1425,81	1718,02	3053,86	Codes PA18B, PA17A, PA16B, PA16A, resp.

intermed wo CC, £							
EA31Z: PCI (0-2 Stents), a suitable code for IABP?, £	2657,37	2657,37	3023,90	3346,61			Codes EA49Z, EA27Z, resp.
Re-expl bleed = major revision, costed thru time use for a major revision, £	180,41	180,411	287,868				A weighted, on/off pump CABG, average of duration of major revisions
Surgical CABG team		**No. in team**	**Hourly cost, £**		**Minute cost, £**		
Surgeons	2		68,54	t_surg_c	1,14	t_surg_min_c	See Labour cost surgical CABG team
Anaesthesists	1		41,90	t_anest_c	0,70	t_anest_min_c	See Labour cost surgical CABG team
Perfusionists	1		24,17	t_perf_c	0,40	t_perf_min_c	See Labour cost surgical CABG team
Anaesthetist nurses	0		27,29	t_n_anest_c	0,45	t_n_anest_min_c	See Labour cost surgical CABG team
Cardic nurses	2		27,29	t_n_card_c	0,45	t_n_card_min_c	See Labour cost surgical CABG team
Physician assistants	0		21,35	t_a_phys_c	0,36	t_a_phys_min_c	See Labour cost surgical CABG team
Total team size, n	6						
Total hourly team cost, £	4,30		257,73		4,30		
Durations							
Minutes	2,35	2,35	1,6	3,1	5		

added to CABG by TTFM, used in model							
Minutes added per on-pump CABG	2,25	2,25	1,5	3			Dr. Kieser, in e-mail
Minutes added per off-pump CABG	2,75	2,75	2	3,5			Dr. Kieser, in e-mail
Minutes added per CABG by TTFM		2,35	5				Dr. Bergsland, oral communications
Duration (min) of minor revision	2,50	2	3	5			Dr. Kieser, in e-mail
*Minor revisions are correcting a twist or kink, cutting an obstructing pericardial edge or reversing a spasm							
Duration (min) of major revision, on-pump	45	45	30	60			Dr. Kieser, in e-mail
Duration (min) of major revision, offpump	30	30	15	45			Dr. Kieser, in e-mail
Weighted mean of on- and off-pump durations(min)	42	42	27	57			
*Major revisions are redoing anastomosis, attaching bypass directly to							

aorta, endarterectomy, replacing arterial with a vein graft							
Rates							
Rate of on-pump CABG	80 %	70 %	90 %				
Rate of off-pump CABG	20 %	30 %	10 %				
Assumption of 3 graft per CABG as a mean	1015	No. of pats=	336	grafts/ pat=	3,021		Dr. Kieser 2010
	609	No. of pats=	200	grafts/ pat=	3,045		Becit 2007
This assumption will be used without sensitivity variation				Mean=	3,030		
Rate of pats with intraoperative revision		0,0417	CI:	0,0203	0,063		Kieser 2010: 14 of 336 patients were revised
Rate of pats with intraoperative revision		0,0900	CI:	0,0339	0,146		Becit 2007: Table 4
Mean rev rate	0,0658	0,0658	0,0658	0,0417	0,0900		
Given revision, rate of simple corrections		0,25					Kieser 2010: 5 revised grafts of 20 were simple
Given revision, rate of simple corrections		0,444					Becit 2007: 3 grafts kinked, 1 twisted of 9 revised
Mean minor rev rate, given	0,347	0,347					Mean of rates

revision							
Given revision, rate of major revisions		0,75					Kieser 2010: 15 revised grafts of 20 vere complex
Given revision, rate of major revisions		0,556					Becit 2007: 2 grafts w/stenosis, 3 grafts poor native coronary vessel
Mean major rev rate, given revision	0,653	0,653					Mean of rates
Rate of patients experiencing MACE postoperatively		7,44 %	CI:	4,90 %	10,80 %		Kieser 2010: 25 patients (of 336) experienced one or more MACEs
Given MACE, mean per-pat number of postoperative MACEs		1,64	CI:				Kieser 2010: 25 patients experienced 41 MACEs
Complications and morbidity rate			w/TTFM	wo/TTFM			
overall morbidity		Morb_w_r	6,0 %	16,0 %	Morb_wo_r		Becit 2007: Table 5
Re-exploration for bleeding		Re_exp_w_b	3,0 %	3,0 %	Re_exP_wo_b		Becit 2007: Table 5
Deep sternal infection		DS_inf_w_r	1,0 %	1,0 %	DS_inf_wo_r		Becit 2007: Table 5
Intra aortic balloon pump (IABP) insertion		IABP_w_r	1,0 %	7,0 %	IABP_wo_r		Becit 2007: Table 5
Peri- or postoperative infarction, text indicates postop MI		MI_w_r	0,0 %	5,0 %	MI_wo_r		Becit 2007: Table 5

Overall mortality, text indicates postop deaths		Mort_w_r	0,0 %	4,0 %	Mort_wo_r		Becit 2007: Table 5
Hospital days to discharge		dur_disch_w	8,2	8,3	dur_disch_wo		Becit 2007
PI>5							
MACE		16,95 %	CI:	8,44 %	28,97 %		Kieser 2010: 10 of 59
Mortallity		11,86 %	CI:	4,91 %	22,93 %		Kieser 2010: 7 of 59
Mortality excl 32 emergency pats		9,26 %	CI:	3,08 %	20,30 %		Kieser 2010: 5 of 54
PI<5							
MACE		5,42 %	CI:	3,06 %	8,77 %		Kieser 2010: 15 of 277
Mortallity		3,25 %	CI:	1,50 %	6,08 %		Kieser 2010: 9 of 277
Mortality excl 32 emergency pats		2,00 %	CI:	0,65 %	4,61 %		Kieser 2010: 5 of 250
Risk of MACE given PI > 5		4,23	CI:	1,69	10,59		Kieser 2010
Other data							
Mean number of grafts per procedure	1,7	1,7	1,5	1,9			Manufacturer Submission document specifies 1.5 to 2 probes per procedure, Table A1
Number of personnel involved in CABG	7,5	7	8				http://www.umm.edu/heart/traditional_cabg_surgery.htm
Surgical CABG							

team							
Number of surgeons		2					http://www.bridgeporthospital.com/heartinstitute/CABG.asp
No. of anesthesiologists		1					Specific numbers given
No. of cardiac perfusionist		1					
No. of physician assistants		2					
No. of nurse anesthetist		1					
No. of cardic nurses		2					
CABG surgery team							
Cardiac surgeon		1					http://www.hcogw.org/newslink/201009cabg.html
Anesthesiologist		1					Numbers given in singular and plural
Perfusionists		2					
Nurses		2					
Physician asistants		2					

6.3.7 Are costs and clinical outcomes extrapolated beyond the study follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified? What assumptions and/or techniques were used for the extrapolation of longer term differences in clinical outcomes between the intervention and its comparator?.

Response

The costs and clinical outcomes are considered to occur either perioperatively or in a period of 1-3 years after CABG. The data available does not give specific data on the time period of observation.

6.3.8 Provide a list of all assumptions in the de novo economic model and a justification for each assumption.

Response

The cost analysis is an initial model that summarizes mean costs per treated patient based on the rate of occurrence of events and resource use during CABG.

6.4 Resource identification, measurement and valuation

All parameters used to estimate cost effectiveness should be presented clearly in a table and include details of data sources. For continuous variables, mean values should be presented and used in the analyses. For all variables, measures of precision should be detailed.

NHS costs

6.4.1 Please describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs and the payment by results (PbR) tariff. Provide the relevant Healthcare Resource Groups (HRG) and PbR codes and justify their selection. Please consider in reference to section 2.

Response

The analysis does not provide overall costs for CABG, only the incremental costs for CABG with and without TTFM. This is possible since the arm under study, CABG with TTFM consists of CABG plus an addition of TTFM. Hence, the resource use of using TTFM and the resource use occurring as a consequence of the TTFM are calculated. Together with costs of treating later events, this is compared to the costs of treating the events seen when TTFM is not used. Only costs of events covered by NHS are included, in addition to the cost of the extra time needed of using TTFM.

6.4.2 Please describe whether NHS reference costs or PbR tariffs are appropriate for costing the intervention being appraised.

Response

In this model, we have distinguished between costs that occur as consequences of performing TTFM and costs that occur as consequences of not performing TTFM. Not all the costs of the CABG procedure have been included. These are cost that would be considered to be the same for both groups, such as the CABG procedure per se. Only costs that might be different for the two groups are included. These would typically be the time and equipment costs associated with TTFM, and the time and costs the use of TTFM might incur or save.

Costs that occur as a consequence of doing TTFM

There are cost implications with regard to extra consumption of time when TTFM is used during CABG. The consumption of time can be divided into the time it takes to perform a TTFM and the time it takes to correct a graft subsequent to TTFM as a result of the clinical information gained from TTFM. These corrections are further divided into minor and major revisions.

The added time used due to measuring transit time flow during CABG surgery is 2.25 minutes for 3 grafts, ref. e-mail from Dr. Kieser. 3 grafts are assumed to be the average number of grafts performed during CABG, ref. papers by Kieser et al. and Becit et al. In order to quantify the cost of the added time to perform TTFM, the added minutes are multiplied with the per-minute labour cost for the surgical team performing the CABG.

The composition of health professionals in the surgical team seems to vary between countries. In the US a surgical team for CABG may consists of two cardiac surgeons, two physician assistants, one anaesthetist, one nurse anaesthetist, two cardiac nurses and one cardiac perfusionist. A total of up to 9 persons may comprise the CABG team. Dr. Bergsland was consulted and he was uncertain whether the US composition of health professionals corresponded to that seen in the UK. Based on his experience the surgical team usually consisted of one lead surgeon, one assistant surgeon, one anaesthetist, one perfusionist and two nurses, i.e. 6 persons. This model assumes that the composition of the surgical team during CABG is as reported by Dr. Bergsland.

In order to calculate the costs of the added time due to TTFM and the subsequent corrections it was necessary to estimate the total labour cost per minute for the surgical team. First, the basic salaries were retrieved from the pay information available from NHS. The basic salary for the surgeons corresponds to that of medical consultants in the NHS[i]. It was assumed that an anaesthetist is a specialty doctor and therefore paid as reported by the NHS as a specialty doctor or a associate specialist [i]. Nurses are eligible for payment according to the NHS Agenda for Change system pay band 6 [ii]. The perfusionist is according to the society of Clinical Perfusion Scientists of Great

Britain and Ireland [iii], paid largely on scales which compare with clinical scientist scales, i.e. pay band 7 [iv]. The basic salaries of the health personnel are multiplied with a labour cost factor to illustrate total labour cost. The UK labour cost factor derives from a UK labour cost survey from 2004[v]. Approximately 34 % is added to the basic salary in order to take into account employers' social security contributions, vocational training costs and other expenditures such as recruitment costs, expenditure on work clothes and employment taxes. Maximum and minimum values for the labour costs are considered in the sensitivity analysis.

Minor revisions due to TTFM are correction of twists or kinks, cutting and obstructing pericardial edge or reversing a spasm. Minor revisions take according to Dr. Kieser on average 2.5 minutes to perform. Dr. Bergsland considered 5 minutes as a potential mean time, ref. oral communication. The estimated rate of these minor revisions is the average rate of intraoperative revisions reported in Kieser 2010 [vi] and Becit 2007 [vii] multiplied with the average rate of minor revisions (0,0658*0,347 = 2,29 %). The added costs of minor revisions due to TTFM is the labour cost of the added minutes work multiplied with the average rate of minor revisions.

Major revisions subsequent to TTFM are redoing anastomosis, attaching bypass directly to aorta, endarterectomy and replacing arterial with vein graft. According to Dr. Kieser the length of the added time to perform major revisions depend on whether the CABG is performed on-pump or off-pump. If the CABG is on-pump, a major revision takes on average 45 minutes. If the CABG is off-pump it takes on average 30 minutes. Given that 80 % of all CABG surgeries in the UK are on-pump the weighted mean duration of time to perform a major revision is 42 minutes. The estimated rate of these major revisions is the average rate of intraoperative revisions reported in Kieser 2010 and Becit 2007 multiplied with the average rate of major revisions (0,0658*0,653 = 4,3 %). The added costs of major revisions subsequent to TTFM is the labour cost of the added minutes work multiplied with the average rate of major revisions.

Costs that occur as a consequence of not doing TTFM

Becit 2007 studied the rate of morbidities with and without TTFM peri and postoperative CABG surgery. As far as we could find, this is the only study that compares CABG with and without TTFM using the technology being assessed. Although other studies, such as Kieser 2010 corroborate the findings, no specific with TTFM/without TTFM data is presented there. Hence, data from this study is used as bases for the clinical events costs. The study by Kim et al. 2010[viii] compared CABG with and without TTFM, however the study was done with older technology than VeriQ and the results were therefore not included in the cost analysis.

The model compares the costs of the morbidities when TTFM is applied during CABG with the costs of the morbidities when TTFM is not utilized. The rates of the morbidities taken from Becit 2007 are multiplied with the cost of treating the morbidities.

The costs of the procedures deep sternal infection, perioperative myocardial infarction and rehab after myocardial infarction are based on the total average costs found in the National Schedule of Reference Cost Year: 2009-2010 NHS HRG data [ix].

We were unable to find a reference costs for the intra aortic balloon pump (IABP). We consulted Dr. Bergsland and he assumed the cost of IABP to correspond to the reference cost for percutaneous coronary intervention (PCI) with 0-2 stents, although the cost of disposables might be somewhat higher. The cost of PCI with 0-2 stents is applied for the cost of IABP in this model

We were unable to find a reference cost that corresponded well to the costs of re-exploration for bleeding. The cost of re-exploration for bleeding is therefore calculated similar to other major revisions, i.e. the labour cost for an average weighted on/off pump major revision (labour cost *42 minutes).

There is some degree of uncertainty associated with the input data of the model. The sensitivity analysis considers the factors thought to be most influential on the outcome costs of the model, for which uncertainty exists. These factors are the time added to the CABG procedure by TTFM, mean number of probes used during the procedure, rate of patients needing revision after TTFM, the relative rate of minor and major revisions, costs of medical interventions needed, the occurrence rate of these clinical events, the size and composition of the CABG team and on-pump rate compared to off-pump.

The factors most affecting the cost level are the number of probes used, the rates of the clinical events that were different for the two groups with and without TTFM, and the cost of the intervention procedures. Compared to the Becit data, rather substantial changes to the input data was needed to get costs that were similar in the two groups.

i. Website. Downloaded 29th of March 2011: http://www.nhscareers.nhs.uk/details/Default.aspx?Id=553

ii. Website. Downloaded 29th of March 2011: http://www.nhscareers.nhs.uk/details/Default.aspx?Id=4

iii. Website. Downloaded 29th of March 2011: http://www.scps.org.uk/index.php?option=com_content&task=view&id=55&Itemid=58

iv. Website. Downloaded 29th of March 2011: http://www.nhscareers.nhs.uk/details/Default.aspx?Id=237

v. Website. Downloaded 29th of March 2011: http://www.statistics.gov.uk/downloads/theme_labour/LabourCostSurvey/LABOUR_COST_SURVEY_04.pdf

vi. Kieser TM, Rose S, Kowalewski R, Belenkie I. Transit-time flow predicts outcomes in coronary artery bypass graft patients: a series of 1000 consecutive arterial grafts. Eur J Cardiothorac Surg 2010;38:155-162.

vii. Becit N, Erkut B, Ceviz M, Unlu Y, Colak A and Kocak H. The impact of intraoperative transit flow measurement on the results of on-pump coronary surgery. European Journal of Cardio-Thoracic Surgery 32 (2007) 313-318.

viii. Kim K-B, Kim JS, Kang H-J, Koo B-K, Kim H-S, Oh B-H and Y-B Park. Ten-year experience with off-pump coronary artery bypass grafting: Lessons learned from early postoperative angiography. The journal of Thoracic and Cardiovascular Surgery. February 2010.

ix. Website. Downloaded 29th of March 2011: http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_123459

Resource identification, measurement and valuation studies

6.4.3 Please provide a systematic search of relevant resource data for the UK. Include a search strategy and inclusion criteria, and consider published and unpublished studies. The search strategy used should be provided as in section 7.9, appendix 9. If the systematic search yields limited UK-specific data, the search strategy may be extended to capture data from non-UK sources. Please give the following details of included studies:

- country of study
- date of study
- applicability to UK clinical practice
- cost valuations used in study
- costs for use in economic analysis
- technology costs.

Response

None of the studies providing data for this analysis has been conducted in the UK. One was conducted in Canada, and the other in Turkey. The unit costs are from the current NHS reference cost and other relevant literature presented in section 6.4.2.

Time resource data has been provided by Dr. Kieser, ref. e-mail dated 21 March 2011.

6.4.4 If clinical experts assessed the applicability of values available, or estimated or adjusted any values, please provide the following details[4]:

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical speciality whose opinion was sought
- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method(s) used to collect and collate the opinions.

The uncertainty around these values should be addressed in the sensitivity analysis.

Response

In total, two experts were consulted. The criterion for consulting Kieser was her extensive experience and her authoring of the Kieser 2010 publication. Dr Bergsland was consulted through t-cons for corroboration. In addition Dr Bergsland was consulted in order for the authors of this document to gain more knowledge on the identified studies he was co-authoring.

Intervention and comparators' costs

6.4.5 Please summarise the cost of each treatment in the following table. Cross-reference to other sections of the submission; for example, technology costs should be cross-referenced to sections 1.9. Provide a rationale for the choice of values used in the cost model discussed in section 6.2.3. Uncertainty around prices in sensitivity analysis.

[4] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

Table B11 Unit costs associated with the technology in the economic model

Labour costs CABG surgical team

A surgical team for standard CABG consists of the following health professionals	**Average annual basic salary (2010)**	**Average annual labour cost (2010)**	**Hourly labour cost (2010)**	**Labour cost per minute (2010) Average**	**Labour cost per minute (2010) Max.**	**Labour cost per minute (2010) Min.**
Cardiac surgeon	£ 87 475	£ 117 154	£ 69	£ 1,14	£ 1,31	£ 0,97
Cardiac surgeon	£ 87 475	£ 117 154	£ 69	£ 1,14	£ 1,31	£ 0,97
Anesthesist	£ 53 467	£ 71 607	£ 42	£ 0,70	£ 0,92	£ 0,48
Cardiac nurse	£ 29 831	£ 39 952	£ 23	£ 0,39	£ 0,45	£ 0,33
Cardiac nurse	£ 29 831	£ 39 952	£ 23	£ 0,39	£ 0,45	£ 0,33
Cardiac perfusionist	£ 35 309	£ 47 288	£ 24	£ 0,40	£ 0,52	£ 0,40
Sum				**£ 4,16**	**£ 4,96**	**£ 3,49**

Ref data:
http://www.nhscareers.nhs.uk/details/Default.aspx?Id=553
http://www.scps.org.uk/index.php?option=com_content&task=view&id=55&Itemid=58
http://www.nhscareers.nhs.uk/details/Default.aspx?Id=237
http://www.statistics.gov.uk/downloads/theme_labour/LabourCostSurvey/LABOUR_COST_SURVEY_04.pdf
http://www.sabp.nhs.uk/policies/alphabetical/D-F/SABP0027%20Flexible%20Working%20Procedure.pdf/

TTFM			
Duration of TTFM for 3 grafts	2,35	Min	
CABG team TTFM cost per patient			10,09
Probes used	1,7	probes	
Probe cost			99,55
Cost of TTFM use			**109,64**

per patient			

See also table B10 for costing data used in this table

Health-state costs

6.4.6 Please summarise, if appropriate, the costs included in each health state (Explanation of definition of health-state). Cross-reference to other sections of the submission for the resource costs. Provide a rationale for the choice of values used in the cost model. The health states should refer to the states in section 6.2.5.

No health states in section 6.2.5 were defined.

Table B12 List of health states and associated costs in the economic model

N/A

Health states	Items	Value	Reference in submission

Adverse-event costs

6.4.7 Please summarise the costs for each adverse event listed in section 5.7 (Adverse events). These should include the costs of therapies identified in section 2.7. Cross-reference to other sections of the submission for the resource costs. Provide a rationale for the choice of values used in the cost model discussed in section 6.2.3. Adverse event and complications episodes. Include all adverse events and complications costs, both during and longer term post-treatment cost.

Table B13 List of adverse events and summary of costs included in the economic model

No Adverse events related to use of the VeriQ is recorded.

Adverse events	Items	Value	Reference in submission

Miscellaneous costs

6.4.8 Please describe any additional costs that have not been covered anywhere else (for example, PSS costs). If none, please state.

Response

All costs covered are in the attached excel file

6.4.9 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

Response

Costs incurred due to mortality have not been substantiated as there is no knowledge of actions taken related to deaths. It is expected that there may be some costs for NHS, these are not taken into account.

6.5 Sensitivity analysis

This section should be read in conjunction with NICE's 'Evaluation Pathway Programme methods guide',

Sensitivity analysis should be used to explore uncertainty around the structural assumptions used in the analysis. Analysis of a representative range of plausible scenarios should be presented and each alternative analysis should present separate results.

The uncertainty around the appropriate selection of data sources should be dealt with through sensitivity analysis. This will include uncertainty about the choice of sources for parameter values. Such sources of uncertainty should be explored through sensitivity analyses.

All inputs used in the analysis will be estimated with a degree of imprecision.

For technologies whose final price/acquisition cost has not been confirmed, sensitivity analysis should be conducted over a plausible range of prices.

6.5.1 Has the uncertainty around structural assumptions been investigated? Provide details of how this was investigated, including a description of the alternative scenarios in the analysis.

Response

The uncertainties around the structural assumptions have not been investigated. The model in itself is very basic due to the small amount of data available. The model could in the future be further developed to include a longer time horizon and more detailed information on the clinical benefits

6.5.2 Was deterministic and/or probabilistic sensitivity analysis undertaken? If not, why not? How variables were varied and what was the rationale for this? Where relevant, the distributions and their sources should be clearly stated. If any parameters or variables listed in section 6.2.7 were omitted from sensitivity analysis, please provide the rationale.

Response

A deterministic sensitivity analysis has been conducted. Some variables were varied according to confidence limits while others were varied according to different NHS cost levels of the procedures. The CABG team size and time

used for TTFM procedures and procedures conducted due to TTFM findings were varied based on input for expert surgeons. Confidence intervals for the rates from the Becit article used in the model have been calculated using the exact binomial distribution. To calculate the costs for the two sensitivity alternative where a proportion for each of the arms are included, one alternative is based on the lower confidence limit for the w/TTFM group and the upper limit for the WO/TTFM group, and vice versa for the other alternative. This is likely a very strict rule and is more extreme than the limits of the bivariate distribution of the proportions. Since some proportions are significantly different from each other, we can assume that the proportion used for the w/TTFM should be less than the one used for wo/TTFM. For the MI and IABP rates, equal midpoint rates have been used in the sensitivity analysis for the second values to accommodate this.

6.6 Results

Provide details of the results of the analysis. In particular, results should include, but are not limited to, the following.

- Costs.
- Disaggregated results such as costs associated with treatment, costs associated with adverse events, and costs associated with follow-up/subsequent treatment.
- A tabulation of the mean cost results.
- Results of the sensitivity analysis

Clinical outcomes from the model

As there is no clinical cost analysis study result, there is no data to compare against the model presented.

6.6.1 For the outcomes highlighted in the decision problem (see section 4), please provide the corresponding outcomes from the model and compare them with clinically important outcomes such as those reported in clinical studies. Discuss reasons for any differences between modelled and observed results (for example, adjustment for cross-over). Please use the following table format for each comparator with relevant outcomes included.

Table B14 Summary of model results compared with clinical data

Outcome	Clinical study result	Model result
Progression-free survival	C_1	R_1
Post-progression survival	C_2	R_2
Overall survival	C_{1+2}	R_{1+2}
Adverse event 1	C_3…	$R_{3...}$
Etc.	…	…

There is no data with which we can compare. The Model put forward here is the only costing analysis we have. No studies have given us data to compare.

6.6.2 Please provide details of the disaggregated costs by health state, and costs by category of cost. Suggested formats are presented below.

Table B15 Summary of costs by health state

As our model does not include health states, this does not apply.

Health state	Cost intervention (X)	Cost comparator (Y)	Increment	Absolute increment	% absolute increment
Health state 1 (HS1)	X_{HS1}	Y_{HS1}	$X_{HS1} - Y_{HS1}$	$\|X_{HS1} - Y_{HS1}\|$	$\|X_{HS1} - Y_{HS1}\|$/ (Total absolute increment)
HS2	X_{HS2}	Y_{HS2}	$X_{HS2} - Y_{HS2}$	$\|X_{HS2} - Y_{HS2}\|$	$\|X_{HS2} - Y_{HS2}\|$/ (Total absolute increment)
…	…	…		…	…
Adverse event 1 (AE1)	X_{AE1}	Y_{AE1}	$X_{AE1} - Y_{AE1}$	$\|X_{AE1} - Y_{AE1}\|$	$\|X_{AE1} - Y_{AE1}\|$/ (Total absolute increment)
AE2	X_{AE2}	Y_{AE2}	$X_{AE2} - Y_{AE2}$	$\|X_{AE2} - Y_{AE2}\|$	$\|X_{AE2} - Y_{AE2}\|$/ (Total absolute increment)
Total	**X_{Total}**	**Y_{Total}**	**$X_{Total} - Y_{Total}$**	**Total absolute increment**	**100%**

Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee

Table B16 Summary of costs by category of cost

	Value	Unit	cost (£)		Value	Unit	Cost (£)			Value	Unit	Cost (£)
TTFM												
Duration of TTFM for 3 grafts	2,35	Min			0	Min				2,35	Min	
CABG team TTFM cost per patient			10,09				0,00					10,09
Probes used	1,7	probes			0	probes				1,7	probes	
Probe cost			99,55				0,00					99,55
Cost of TTFM use per patient			**109,64**				**0,00**					**109,64**
Consequences of TTFM use												
Revision rate, %	6,58 %				0,00 %					6,58 %		
Minor revisions, %	2,29 %				0,00 %					2,29 %		
Major revisions, %	4,30 %				0,00 %					4,30 %		
Duration of minor revisions	2,5	Min			0	Min				2,5	Min	
Rate of minor revisions	2,29 %				0,00 %					2,286 %		
CABG team cost for minor revisions			10,74				0,00					10,74

Team cost of minor revision per patient			**0,25**				**0,00**					**0,25**
Duration of major revisions	42,0	Min			0,0	Min				42,0	Min	
Rate of major revisions	4,30 %				0,00 %					4,30 %		
CABG team cost for major revisions			180,41				0,00					180,41
Team cost of major revision per patient			**7,75**				**0,00**					**7,75**
Sum of TTFM costs			**117,64**				**0,00**					**117,64**
Consequences of not doing TTFM												
Intraoperative issues:												
Re-exploration of bleeding, rate	3,00 %				3,00 %					0,00 %		
Re-exploration of bleeding, cost			180,41				180,41					0,00
Per patient cost, re-exploration of bleeding			**5,41**				**5,41**					**0,00**
Deep sternal	1,00 %				1,00 %					0,00 %		

infection, rate												
Deep sternal infection, cost			860,55				860,55					0,00
Per patient cost, DS infection			**8,61**				**8,61**					**0,00**
IABP, rate	1,00 %				7,00 %					-6,00 %		
IABP, cost			2657,37				2657,37					0,00
Per patient cost, IABP			**26,57**				**186,02**					**-159,44**
Postoperative issues:												
Perioperative MI, rate	0,00 %				5,00 %					-5,00 %		
Perioperative MI, cost			1415,20				1415,20					0,00
Rehab after MI, cost			251,76				251,76					0,00
Per patient cost, MI			**0,00**				**83,35**					**-83,35**
Sum of consequence costs			**40,59**				**283,38**					**-242,79**
Sum of all costs			**158,23**				**283,38**					**-125,15**

Base-case analysis

6.6.3 Please present your results in the following table. List interventions and comparator(s) from least to most expensive.

Table B17 Base-case results

Technology	**Total costs (£) cost to use**
TTFM VeriQ	109,64
Clinical Assessment	0,00
Technology	**Total costs (£) cost consequenses**
TTFM VeriQ	40,59
Clinical Assessment	283,38

Sensitivity analyses

Please present results of deterministic sensitivity analysis. Consider the use of tornado diagrams.

Variable values										
Variable	**First value**		**Base value**	**Second value**		**Delta Cost values, £**				**Width of interval, £**
Duration of TTFM per procedure, min		2	2,35	5		-126,65	-125,15	-113,76		12,89
Mean No. of probes per procedure		1,4	1,7	2		-142,71	-125,15	-107,58		35,14
Rate of pats with revisions		2,20 %	6,58 %	14,60 %		-130,47	-125,15	-115,41		15,07
Duration of minor revisions, min		2	2,5	5		-125,20	-125,15	-124,90		0,29
Duration of major revisions, min		27	42	57		-127,92	-125,15	-122,38		5,54
Relative rate of minor revisions		50,0 %	34,7 %	20,0 %		-126,85	-125,15	-123,50		3,35
Re-operative procedures, cost (£)		80,00	180,41	288,0 0		-125,15	-125,15	-125,15		0,00
Re-operative procedures, rates	0,6 %	8,5 %	3,0 %	8,5 %	0,6 %	-139,40	-125,15	-110,89		28,50
Deep sternal infection, cost (£)		687,00	860,55	1425, 00		-125,15	-125,15	-125,15		0,00
Deep sternal infection, rates	0,0 %	5,5 %	1,0 %	5,5 %	0,0 %	-171,79	-125,15	-78,51		93,28
IABP, cost (£)		3346,0 0	2657,3 7	1968, 00		-166,47	-125,15	-83,79		82,68
IABP, rates	0,0 %	13,9 %	1,0 %	3,5 %	3,5 %	-334,02	-125,15	34,29		368,31
MI, costs (£)		2067,0 0	1666,9 6	1267, 00		-145,15	-125,15	-105,15		40,00

MI, rates	0,0 %	11,3 %	0,0 %	2,5 %	2,5 %	-229,83	-125,15	-48,09		181,74
Cost of CABG team composition,(£)		2,70	4,30	5,15		-131,87	-125,15	-121,53		10,34
On-pump rate		70,0 %	80,0 %	90,0 %		-125,21	-125,15	-125,09		0,12

6.6.4

Please present the results of PSA.

Response

N/A

6.6.5 Please present the results of scenario analysis. Include details of structural sensitivity analysis.

Response

The results of the Scenario analysis are to be found in table B16. The scenario compares the use of TTFM against not using it, and adopting clinical analysis. Due to TTFM allowing for intraoperative graft revision, this gives a reduction in post-operative complications, MACE etc. Although not totally negating all post operative complications, the reduction is significant enough to make TTFM with VeriQ cost effective over clinical analysis.

Below are the tables of each sensitivity analysis.

Sensitivity analysis									
CABG with TTFM	**CABG without TTFM**	**Difference**	**Sensitivity variable**						
158,23	**283,38**	**-125,15**	**Base costs**		Sens. value 1	Sens. value 2		Base value 1	Base value 2
169,62	283,38	-113,76	Duration of TTFM per procedure, min		5			2,35	
175,80	283,38	-107,58	Mean No. of probes per procedure		2			1,7	
167,97	283,38	-115,41	Rate of pats with revisions		14,60 %			6,58 %	
158,48	283,38	-124,90	Duration of minor revisions, min		5			2,5	
161,00	283,38	-122,38	Duration of major revisions, min		57			42	
159,88	283,38	-123,50	Relative rate of minor revisions		20,0 %			34,7 %	
161,46	286,61	-125,15	Re-operative procedures, cost (£)		288,00			180,41	
168,19	279,09	-110,89	Re-operative procedures, rates		8,5 %	0,6 %		3,0 %	3,0 %
163,88	289,03	-125,15	Deep sternal infection, cost (£)		1425,00			860,55	
196,53	275,03	-78,51	Deep sternal infection, rates		5,5 %	0,0 %		1,0 %	1,0 %
151,34	235,13	-83,79	IABP, cost (£)		1968,00			2657,37	
224,67	190,37	34,29	IABP, rates		3,5 %	3,5 %		1,0 %	7,0 %
158,23	263,38	-105,15	MI, costs (£)		1267,00			1666,96	
193,61	241,71	-48,09	MI, rates		2,5 %	2,5 %		0,0 %	5,0 %
			CABG team composition		Number of:				
					2	Surgeons		2	
					1	Anaesthesists		1	
					2	Perfusionists		1	
					1	Nurse anaesthetists		0	
					2	Cardiac nurses		2	
					0	Physician assistants		0	
161,85	283,38	-121,53	Cost of CABG team composition, (£)		5,15	Minutely team cost, (£)		4,30	

158,30	283,38	-125,09	On-pump rate		0,90			0,80	

Sensitivity analysis									
CABG with TTFM	**CABG without TTFM**	**Difference**	**Sensitivity variable**						
158,23	**283,38**	**-125,15**	**Base costs**		Sens. value 1	Sens. value 2		Base value 1	Base value 2
156,73	283,38	-126,65	Duration of TTFM per procedure, min		2			2,35	
140,67	283,38	-142,71	Mean No. of probes per procedure		1,4			1,7	
152,91	283,38	-130,47	Rate of pats with revisions		2,20 %			6,58 %	
158,19	283,38	-125,20	Duration of minor revisions, min		2			2,5	
155,47	283,38	-127,92	Duration of major revisions, min		27			42	
156,53	283,38	-126,85	Relative rate of minor revisions		50,0 %			34,7 %	
155,22	280,37	-125,15	Re-operative procedures, cost (£)		80,00			180,41	
153,94	293,34	-139,40	Re-operative procedures, rates		0,6 %	8,5 %		3,0 %	3,0 %
156,50	281,65	-125,15	Deep sternal infection, cost (£)		687,00			860,55	
149,89	321,68	-171,79	Deep sternal infection, rates		0,0 %	5,5 %		1,0 %	1,0 %
165,12	331,59	-166,47	IABP, cost (£)		3346,00			2657,37	
132,46	466,47	-334,02	IABP, rates		0,0 %	13,9 %		1,0 %	7,0 %
158,23	303,38	-145,15	MI, costs (£)		2067,00			1666,96	
158,23	388,07	-229,83	MI, rates		0,0 %	11,3 %		0,0 %	5,0 %
			CABG team composition		Number of:				
					1	Surgeons		2	
					1	Anaesthesists		1	
					1	Perfusionists		1	
					0	Nurse anaesthetists		0	
					1	Cardiac nurses		2	
					0	Physician assistants		0	
151,51	283,38	-131,87	Cost of CABG team composition, (£)		2,70	Minutely team cost, (£)		4,30	

158,17	283,38	-125,21	On-pump rate		0,70			0,80	

6.6.6 What were the main findings of each of the sensitivity analyses?

Response

The main findings of the sensitivity analyses are that even when the max/min variables are entered, that TTFM nearly always gives a more cost effective result than not using TTFM.

See also paragraph 6.4.2

See table included in 6.6.3 sensitivity analysis results

6.6.7 What are the key drivers of the cost results?

Response

Material use (probes), adverse event percentages and costs involved. Added costs of surgical team were minimal in relation to the added cost of adverse events, reinterventions, reoperations and post operative complications.

Please also see paragraph 6.4.2

Validation

6.6.8 Please describe the methods used to validate and quality assure the model. Provide references to the results produced and cross-reference to evidence identified in the clinical and resources sections.

Response

As there are no clinical studies to validate the data with, we are relying on publicly available information for the source of cost data, and clinical evidence is based on studies referred to and consultations with surgeons specialising in the cardiac field.

All sources referred to are openly listed throughout this document.

6.7 Subgroup analysis

For many technologies, the capacity to benefit from treatment will differ for patients with differing characteristics.

Types of subgroups that are not considered relevant are those based solely on the following factors.

- Subgroups based solely on differential treatment costs for individuals according to their social characteristics.
- Subgroups specified in relation to the costs of providing treatment in different geographical locations within the UK (for example, when the costs of facilities available for providing the technology vary according to location).

6.7.1 Please specify whether analysis of subgroups was undertaken and how these subgroups were identified. Were they identified on the basis of an a priori expectation of differential clinical effectiveness or cost due to known, biologically plausible, mechanisms, social characteristics or other clearly justified factors? Cross-reference the response to section 5.3.7.

Response

N/A No subgroups were analysed.

6.7.2 Please clearly define the characteristics of patients in the subgroup.

Response

N/A No subgroups were analysed.

6.7.3 Please describe how the statistical analysis was undertaken.

Response

N/A No subgroups were analysed.

6.7.4 What were the results of the subgroup analysis/analyses, if conducted? Please present results in a similar table as in section 6.6.3 (Base-case analysis).

Response

N/A No subgroups were analysed.

6.7.5 Were any obvious subgroups not considered? If so, which ones, and why were they not considered? Please refer to the subgroups identified in the decision problem in section 4.

Response

N/A No subgroups were analysed.

6.8 Interpretation of economic evidence

6.8.1 Are the results from this cost analysis consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?

Response

There is no published economic literature to perform a comparison and assess for consistency

6.8.2 Is the cost analysis relevant to all groups of patients who could potentially use the technology as identified in the decision problem in section 4?

Response

Yes.

6.8.3 What are the main strengths and weaknesses of the analysis? How might these affect the interpretation of the results?

Response

6.8.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

Response

References

Please use a recognised referencing style, such as Harvard or Vancouver.

Response

References are placed at the end of each page for ease of use. Where references are used, the source will be listed at the bottom of the applicable page.

7 Appendices

7.1 Appendix 1

7.1.1 IFU, scientific discussion or drafts.

7.2 Appendix 2: Search strategy for section 5.1 (Identification of studies)

The following information should be provided.

7.2.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library.

Response

The Above databases were searched, in addition to this we have searched our own database of published studies.

7.2.2 The date on which the search was conducted.

Response

Search was conducted 15 february 2011

7.2.3 The date span of the search.

Response

Date Span – 1 jan 2004 to 15 feb 2011

7.2.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example,

MeSH) and the relationship between the search terms (for example, Boolean).

Response

#13: ((#12) AND "2004"[Publication Date] : "2011"[Publication Date])
#12: #7 and #11
#11: #8 or #9 or #10
#10: “coronary artery bypass”
#9: “coronary artery graft”
#8: CABG
#7: #1 or #2 or #3 or #4 or #5 or #6
#6: pi or mf
#5: "mean flow"
#4: "pulsatility index"
#3: ttf or ttm
#2: transit-time
#1: “transit time flow”

Searches #1 - #6, pooled in #7 focuses on TTFM type of measurements, while searches #8 - #10 selects articles on or referring to CABG, pooled in search #11.

Search #12 find the articles that satisfy both search #7 and #11. Search #13 selected the articles published in 2004 or later.

A manual search was then conducted to exclude studies with data collection pre VeriQ launch in 2004, and that did not use VeriQ, and that used TTFM or VeriQ as a Control method in a study of surgical strategy comparisons. Foreign language studies, case studies, Editor letters were also removed.

7.2.5 Details of any additional searches, such as searches of company databases (include a description of each database).

Response

MediStim has continuously strived to keep updated on studies published with TTFM and its comparators. We therefore conducted a search of our own database of Studies and published articles to include in the clinical evidence.

7.2.6 The inclusion and exclusion criteria.

Response

Inclusion:

- Published 2004 or later.
- CABG patients

Exclusion

-

7.2.7 The data abstraction strategy.

Response

7.3 Appendix 3: Quality assessment of RCT(s) and non-RCT(s) (section 5.4)

7.3.1 A suggested format for the quality assessment of RCT(s) is shown below.

Study ID or acronym		
Study question	**How is the question addressed in the study?**	**Grade (yes/no/not clear/N/A)**
Was randomisation carried out appropriately?		
Was the concealment of treatment allocation adequate?		
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?		
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?		
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?		
Is there any evidence to suggest that the authors measured more outcomes than they reported?		
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?		
Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

Study ID or acronym **Becit 2007** **Becit N, Erkut B, Ceviz M, Unlu Y, Colak A, and Kocak H. The impact of intraoperative transit time flow measurement on th results of on-pump coronary surgery. European Journal of Cardio-thoratic Surgery 32 (2007) 313-318** **The purpose of the study was to evaluate the effect of detection of graft dysfunction by intraoperative TTFH on the surgical results of on-pump CABG.**		
Study question	**How is the question addressed in the study?**	**Grade (yes/no/not clear/N/A)**
Was randomisation carried out appropriately?	Patients were not randomized. A transit flow meter (MediStim VQ-1101) became available in February 2006. The last 100 consecutive patients before this date formed the control group (group A), and the first 100 consecutive patients after this date formed the study group (group B).	N/A
Was the concealment of treatment allocation adequate?		N/A
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	The baseline data (age, gender, smking, arterial hypertention, diabetes mellitus, hypercholesterolemia, old myocardial infarction, peripheral arterial disease, COPD, coronary lesions, LVEF%, urgent operations, EuroScore, distribution of number of grafts, mean number of grafts, Number of distal anastomosis by vessel type, number of grafts by graft type) showed no significant differences between group A and B. The incidence of variables that can influence the clinical results was similar in both groups ($p>0.05$). There was no significant difference in Euroscore (Group A 4.24 and Group B 4.30).	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	This study evaluates a method for transit time flow measurement and requires the use of a transit flow meter. Therefore care providers could not be blinded. Whether the participants and outcome assessors were blinded is not clearly stated. As this is a study comparing the last 100 patients before a change in treatment procedure and the 100 first after, the blinding of patients was probably not an issue.	Not clear
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	There were no drop-outs. As the device is used intraoperatively, and not over an extended period of time, it is difficult for patients to drop out or be excluded from the study data.	No

Is there any evidence to suggest that the authors measured more outcomes than they reported?	There is no reason to suggest that outcomes were measured and not reported. The authors present results on the data provided through TTFM and report both significant and non-significant endpoints.	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	There is no indication that not all 100 patients in each group are included in the analysis.	N/A
Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

Study ID or acronym:

Kieser 2010

Kieser TM, et al. Transit-time flow predicts outcomes in coronary artery bypass graft patients: a series of 1000 consecutive arterial grafts. Eur J Cardiothorac Surg (2010).

In this study, TTF was used in 336 consecutive patients to assess the value of this method in predicting postoperative major adverse cardiac events (MACEs). Their findings suggest that the pulsatility index (PI), one of three TTF measurements, is highly predictive of outcomes.

Study question	**How is the question addressed in the study?**	**Grade (yes/no/not clear/N/A)**
Was randomisation carried out appropriately?	The study is a retrospective analysis of data from consecutive patients of a single surgeon. There was no randomization in this study. Patients were divided into two groups, presumed high and low risk of future events, based on the values for each of the variables pulsatility index (PI), their flow rate and their diastolic filling (DF).	N/A
Was the concealment of treatment allocation adequate?	A single surgeon in whom TTF was first used at LIBIN Cardiovascular Institute of Alberta in Canada for bypass graft assessment intraoperatively.	N/A
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Patients were divided into two groups based on PI, flow and DF and were therefore not similar in terms of prognostic factors.	N/A
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	There was no blinding in this study. This study is a retrospective analysis of data from consecutive patients entered into a provincial database. All patients were undergoing standard procedures.	No
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No indication of patients not included in the analysis. All patients were registered with PI and flow measurements, while 9% of patients did not have DF values due to unacceptable EKG trace.	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Both significant and non-significant results are presented. PI flow and DF are the standard TTF measurements, MACE and mortality are the most important events outcomes.	No

Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	The analyses were performed on all patients until 1000 arterial grafts were reached; between April 2004 and April 2007.	Yes
Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

Study ID or acronym **Jokinen 2010** **Jokinen JJ, et al. Clinical value of intra-operative transit-time flow measurement for coronary artery bypass grafting: a prospective angiography-controlled study. Eur J Cardiothorac Surg (2010)** In this study, the predictive value of the TTFM in CABG patients was assessed prospectively with regard to short-term graft patency and long-term patient survival. The patients underwent primary elective CABG between March 2001 and December 2002 using the VeriQ system.		
Study question	**How is the question addressed in the study?**	**Grade (yes/no/not clear/N/A)**
Was randomisation carried out appropriately?	Prospective study, no randomisation. 75 Patients (with 204 consecutive grafts) recruited in conjunction with a proximal anastomotic device evaluation study.	N/A
Was the concealment of treatment allocation adequate?	All patients / grafts treated (APT) : CABG and TTMF.	N/A
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	No control group. TTMF, transit-time mean-flow is different in coronary arteries: RCA (right coronary artery) has higher PI (Pulsatility Index, p=0.007) than LAD (Left anterior descendent artery) Section 3.1: “The variability of the measurements was generally rather wide, which may have affected the occurrence of statistically significant differences”	Not clear
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	The only blinding was for Independent Senior Cardiologist who was blinded to the patient data and assessed the angiographies 6 months after CABG	Yes
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	The 6-month occlusion grade verified by coronary angiography was 15%, as expected from other studies.	N/A
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Both significant and non-significant results are presented. Findings similar and dissimilar to other studies presented.	No

Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	APT analysis of all existing data. No substitutions for missing values.	No
Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

Study ID or acronym: **Nordgaard 2009** **Nordgaard HB et al. Pulsatility index variations using two different transit-time flowmeters in coronary artery bypass surgery. Eur J Cardiothorac Surg (2009)** This study may not be relevant as it does not look at clinical outcomes, but compares flow and PI measurements from two TTFM systems used on the same grafts.		
Study question	**How is the question addressed in the study?**	**Grade (yes/no/not clear/N/A)**
Was randomisation carried out appropriately?	Prospective comparison of PI and flow values from two flowmeters: MediStim or Transonic. Own study 1: Assessment of PI in the same graft by MediStim and Transonic flowmeters: TTMF was measured simultaneously using the two flowmeters in 19 coronary bypass grafts. Own study 2: Assessment of PI during different filter settings: 8 grafts in 4 patients.	N/A
Was the concealment of treatment allocation adequate?	Treatment allocation equal for all 10 patients operated on by the same surgeon.	N/A
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Each measurement was done at a stable haemodynamic condition after weaning from cardiopulmonary bypass. Intra patient variation measured.	Own studies: Yes
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Open and equal treatment for all participants in the own study	No
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No drop-outs due to nature of the study	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No. The two flowmeters do not produce different parameters, TTMF and the estimated PI (pulsatility index). The difference in PI between the flowmeters seems to depend both on type of filter and the type of artery. The impact of the latter is unclear.	Unclear

Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	All patients treated (APT) analyzed measured	No
Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

Response

7.4 Appendix 4: Search strategy for section 5.7 (Adverse events)

The following information should be provided.

7.4.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library.

Response

No Known Adverse events were found, or have ever been recorded with VeriQ

7.4.2 The date on which the search was conducted.

Response

15th feb 2011

7.4.3 The date span of the search.

Response

01/01/2004 to 15/02/2011

7.4.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Response

As we are a device Manufacturer, Adverse events pertaining to our Technology are reported directly to us, as Health institutions are obliged to report any adverse events with intraoperative devices directly to the manufacturer. This has never occurred, nevertheless the following criteria were searched, and no relevant articles were found:

CABG AND TTFM AND adverse event

CABG AND Transit time flow AND adverse event

Transit time Flow AND coronary AND adverse event

Transit time AND Coronary graft AND Adverse event

7.4.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

Response

No studies in our own database refer to adverse events with VeriQ

7.4.6 The inclusion and exclusion criteria.

Response

7.4.7 The data abstraction strategy.

Response

7.5 Appendix 5: Quality assessment of adverse event data in section 5.7 (Adverse events)

7.5.1 Please tabulate the quality assessment of each of the non-RCTs identified.

Response

n/a

7.6 Appendix 6: Search strategy for cost-effectiveness and cost studies (section 6.1)

The following information should be provided.

7.6.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- EconLIT
- NHS EED.

Response

To retrieve relevant health economics papers, a search were performed on the 17th of March 2011 using the service provider OvidSP. OvidSP comprise more than hundred databases, among them Embase, Econlit, EBM Reviews, Medline ® and Medline ® In-Process. In addition, a literature search was performed on the 23rd of March 2011 using a selection of databases provided by Proquest Dialog Datastar. The selection of databases were the following; Cochrane, Lancet Titles, Cochrane, Allied & Complementary Medicine™,British Library Inside Conferences, DH-DATA: Health Administration, Medical Toxicology & Environmental Health, ERIC, ESPICOM Pharmaceutical & Medical Device News, Gale Group Health Periodicals Database, Gale Group PROMT®, International Pharmaceutical Abstracts,

MEDLINE® and Polymer Library. A literature search was also conducted on the 17th of March in the NHS EED database.

7.6.2 The date on which the search was conducted.

Response

17th and 23rd of March 2011

7.6.3 The date span of the search.

Response

No limit was set

7.6.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Response

The search terms were consistently used in all relevant search engines, i.e. the terms and the order of the terms was the same. The following search terms and structure were used:

1. coronary artery bypass
2. coronary artery graft
3. cabg
4. transit time
5. transit-time
6. ttf
7. ttfm
8. economic
9. cost
10. #1 or #2 or #3
11. #4 or #5 or #6 or #7
12. #8 or #9
13. #10 and #11 and #12

7.6.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

Response

A Similar search was performed on internal database of the manufacturer. No results were found.

7.7 Appendix 7: Quality assessment of cost-effectiveness and cost studies (section 6.1)

N/A

	Study name	
Study question	**Grade (yes/no/not clear/N/A)**	**Comments**
Study design		
1. Was the research question stated?		
2. Was the economic importance of the research question stated?		
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?		
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?		
5. Were the alternatives being compared clearly described?		
6. Was the form of economic evaluation stated?		
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?		
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?		

9. Were details of the design and results of the effectiveness study given (if based on a single study)?		
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?		
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?		
12. Were the methods used to value health states and other benefits stated?		
13. Were the details of the subjects from whom valuations were obtained given?		
14. Were productivity changes (if included) reported separately?		
15. Was the relevance of productivity changes to the study question discussed?		
16. Were quantities of resources reported separately from their unit cost?		
17. Were the methods for the estimation of quantities and unit costs described?		
18. Were currency and price data recorded?		
19. Were details of price adjustments for inflation or currency conversion given?		
20. Were details of any model used given?		
21. Was there a justification for the choice of model used and the key parameters on which it was based?		
Analysis and interpretation of results		
22. Was the time horizon of cost and benefits stated?		
23. Was the discount rate stated?		
24. Was the choice of rate justified?		

25. Was an explanation given if cost or benefits were not discounted?		
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?		
27. Was the approach to sensitivity analysis described?		
28. Was the choice of variables for sensitivity analysis justified?		
29. Were the ranges over which the parameters were varied stated?		
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)		
31. Was an incremental analysis reported?		
32. Were major outcomes presented in a disaggregated as well as aggregated form?		
33. Was the answer to the study question given?		
34. Did conclusions follow from the data reported?		
35. Were conclusions accompanied by the appropriate caveats?		
36. Were generalisability issues addressed?		
Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

7.8 Appendix 8: Search strategy for section 6.4 (Measurement and valuation of health effects)

The following information should be provided.

7.8.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline

- Embase
- Medline (R) In-Process
- NHS Economic Evaluation Database (NHS EED)
- EconLIT.

Response

None of the studies providing data for this analysis has been conducted in the UK. One was conducted in Canada, and the other in Turkey. The unit costs are from the current NHS reference cost and other relevant literature presented in section 6.4.2.

Please see section 6.4 for data extracted and results.

7.8.2 The date on which the search was conducted.

Response

N/A

7.8.3 The date span of the search.

Response

N/A

7.8.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Response

N/A

7.8.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

Response

N/A

7.8.6 The inclusion and exclusion criteria.

Response

N/A

7.8.7 The data abstraction strategy.

Response

N/A

7.9 Appendix 9: Resource identification, measurement and valuation (section 6.4)

The following information should be provided.

7.9.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- NHS EED
- EconLIT.

Response

The search strategies are outlined in 7.6 and 6.4

7.9.2 The date on which the search was conducted.

Response

See 7.6 and 6.4

7.9.3 The date span of the search.

Response

See 7.6 and 6.4

7.9.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Response

See 7.6 and 6.4

7.9.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

Response

See 7.6 and 6.4

7.9.6 The inclusion and exclusion criteria.

Response

See 7.6 and 6.4

7.9.7 The data abstraction strategy.

Response

See 7.6 and 6.4

8 Related procedures for the submission of evidence

8.1 Cost models

An electronic executable version of the cost model should be submitted to NICE with the full submission.

NICE accepts executable cost models using standard software – that is, Excel, TreeAge Pro, R or WinBUGs. If you plan to submit a model in a non-standard package, NICE should be informed in advance. NICE, in association with the EAC, will investigate whether the requested software is acceptable, and establish if you need to provide NICE and the EAC with temporary licences for the non-standard software for the duration of the assessment. NICE reserves the right to reject cost models in non-standard software. A fully executable electronic copy of the model must be submitted to NICE with full access to the programming code. **Care should be taken to ensure that the submitted versions of the model programme and the written content of the evidence submission match.**

NICE may distribute the executable version of the cost model to a consultee if they request it. If a request is received, NICE will release the model as long as it does not contain information that was designated confidential by the model owner, or the confidential material can be redacted by the model owner without producing severe limitations on the functionality of the model. The consultee will be advised that the model is protected by intellectual property rights, and can be used only for the purposes of commenting on the model's reliability and informing comments on the MTCD.

Manufacturers and sponsors must ensure that all relevant material pertinent to the decision problem has been disclosed to NICE at the time of submission. NICE may request additional information not submitted in the original submission of evidence. Any other information will be accepted at NICE's discretion.

When making a full submission, manufacturers and sponsors should check that:

- an electronic copy of the submission has been given to NICE with all confidential information highlighted and underlined
- an executable electronic copy of the cost model has been submitted
- the checklist of confidential information (provided by NICE) has been completed and submitted.

8.2 Disclosure of information

To ensure that the assessment process is as transparent as possible, NICE considers it highly desirable that evidence pivotal to the Medical Technologies Advisory Committee's decisions should be publicly available at the point of issuing the MTCD and MTG.

Under exceptional circumstances, unpublished evidence is accepted under agreement of confidentiality. Such evidence includes 'commercial in confidence' information and data that are awaiting publication ('academic in confidence').

When data are 'commercial in confidence' or 'academic in confidence', it is the manufacturer's or sponsor's responsibility to highlight such data clearly, and to provide reasons why they are confidential and the timescale within which they will remain confidential. The checklist of confidential information should be completed: if it is not provided, NICE will assume that there is no confidential information in the submission. It is the responsibility of the manufacturer or sponsor to ensure that the confidential information checklist is kept up to date.

It is the responsibility of the manufacturer or sponsor to ensure that any confidential information in their evidence submission is clearly underlined and highlighted correctly. NICE is assured that information marked 'academic in confidence' can be presented and discussed during the public part of the Appraisal Committee meeting. NICE is confident that such public presentation does not affect the subsequent publication of the

information, which is the prerequisite allowing for the marking of information as ‘academic in confidence’.

Please therefore underline all confidential information, and highlight information that is submitted under ‘commercial in confidence’ in blue and information submitted under ‘academic in confidence’ in yellow.

NICE will ask manufacturers and sponsors to reconsider restrictions on the release of data if there appears to be no obvious reason for the restrictions, or if such restrictions would make it difficult or impossible for NICE to show the evidential basis for its guidance. Information that has been put into the public domain, anywhere in the world, cannot be marked as confidential.

Confidential information submitted will be made available for review by the EAC and the MTAC. NICE will at all times seek to protect the confidentiality of the information submitted, but nothing will restrict the disclosure of information by NICE that is required by law (including in particular, but without limitation, the Freedom of Information Act 2000).

The Freedom of Information Act 2000, which came into force on 1 January 2005, enables any person to obtain information from public authorities such as NICE. The Act obliges NICE to respond to requests about the recorded information it holds, and it gives people a right of access to that information. This obligation extends to submissions made to NICE. Information that is designated as ‘commercial in confidence’ may be exempt under the Act. On receipt of a request for information, the NICE secretariat will make every effort to contact the designated company representative to confirm the status of any information previously deemed ‘commercial in confidence’ before making any decision on disclosure.

8.3 Equity and equality

NICE is committed to promoting equality and eliminating unlawful discrimination, including paying particular attention to groups protected by equalities legislation. The scoping process is designed to identify groups who are relevant to the appraisal and reflect the diversity of the population. NICE

consults on whether there are any issues relevant to equalities within the scope of the appraisal, or if there is information that could be included in the evidence presented to the Appraisal Committee to enable them to take account of equalities issues when developing guidance.

Evidence submitters are asked to consider whether the chosen decision problem could be impacted by NICE's responsibility in this respect, including when considering subgroups and access to recommendations that use a clinical or biological criterion.

For further information, please see the NICE website (www.nice.org.uk/aboutnice/howwework/NICEEqualityScheme.jsp).

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[i] Website. Downloaded 29th of March 2011: http://www.nhscareers.nhs.uk/details/Default.aspx?Id=553

[ii] Website. Downloaded 29th of March 2011: http://www.nhscareers.nhs.uk/details/Default.aspx?Id=4

[iii] Website. Downloaded 29th of March 2011: http://www.scps.org.uk/index.php?option=com_content&task=view&id=55&Itemid=58

[iv] Website. Downloaded 29th of March 2011: http://www.nhscareers.nhs.uk/details/Default.aspx?Id=237

[v] Website. Downloaded 29th of March 2011: http://www.statistics.gov.uk/downloads/theme_labour/LabourCostSurvey/LABOUR_COST_SURVEY_04.pdf

[vi] Kieser TM, Rose S, Kowalewski R, Belenkie I. Transit-time flow predicts outcomes in coronary artery bypass graft patients: a series of 1000 consecutive arterial grafts. Eur J Cardiothorac Surg 2010;38:155-162.

[vii] Becit N, Erkut B, Ceviz M, Unlu Y, Colak A and Kocak H. The impact of intraoperative transit flow measurement on the results of on-pump coronary surgery. European Journal of Cardio-Thoracic Surgery 32 (2007) 313-318.

[viii] Kim K-B, Kim JS, Kang H-J, Koo B-K, Kim H-S, Oh B-H and Y-B Park. Ten-year experience with off-pump coronary artery bypass grafting: Lessons learned from early postoperative angiography. The journal of Thoracic and Cardiovascular Surgery. February 2010.

[ix] Website. Downloaded 29th of March 2011: http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_123459