EXTERNAL ASSESSMENT CENTRE REPORT

Title: VeriQ system for assessment of graft flow during coronary artery bypass graft

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Declared interests of the authors

None

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of NICE. Any errors are the responsibility of the authors.

Contents

Abbreviations

BF	Backwards Flow
CABG	Coronary Artery Bypass Graft
CAD	Coronary Artery Disease
CHD	Coronary Heart Disease
DF	Diastolic Filling
DRG	Diagnosis Related Groups (HRG in England)
EAC	External Assessment Centre
ESC/EACTS	European Society of Cardiology/ European Association of Cardio-Thoracic Surgeons
FFT	Fast Fourier Transform
HRG	Healthcare Resource Group
IFI	Intra-operative Fluorescence Imaging
IABP	Intra aortic balloon pump
MACE	Major Adverse Cardiac Events
MeSH	Medical Subject Headings
MF	Mean Flow
MGF	Mean Graft Flow
MI	Myocardial infarction
NICE	National Institute for Health and Clinical Excellence
OPCAB	Off-pump Coronary Artery Bypass
PbR	Payment by Results
PI	Pulsatility Index
RCT	Randomised Controlled Trial
TTFM	Transit Time Flow Measurement or Transit Time Flowmeter

Notes on use of page numbers, etc

Page numbers, tables, etc, from the manufacturer's submission are marked in or from 'the manufacturer's submission'.

Page numbers, tables, etc, in this report are marked 'in this report'.

Notes on appendices

Four appendices listing references and one appendix with tables of cost analysis data are provided.

1 Summary

1.1 *Scope of the submission*

This report assesses the submission to NICE by the manufacturer (MediStim ASA) covering the use of the VeriQ transit time flowmetry system during surgery for assessing graft flow. More specifically, the manufacturer's submission considers the VeriQ system used for the intra-operative assessment of graft flow for patients undergoing coronary artery bypass surgery, which is in line with the scoping document issued by NICE for this appraisal. This report includes an assessment of both the clinical effectiveness and the cost implications, based on evidence submitted by the manufacturer.

1.2 *Summary of submitted clinical effectiveness evidence*

Four studies and one guidelines document were included in the manufacturer's submission evidence for clinical effectiveness, relating to patients undergoing coronary artery bypass. The four studies were all observational studies (level 2b studies; ref: Oxford Centre for Evidence-Based Medicine - Levels of Evidence). The included guidelines were the European Society of Cardiology and the European Association of Cardio-Thoracic Surgeons (ESC/EACTS) guidelines on myocardial revascularisation. None of these studies were funded by the manufacturer MediStim ASA or by any other manufacturer.

Three of the studies investigated the peri or post-operative outcomes and major adverse cardiac events (MACE) associated with graft failure in patients who underwent coronary artery bypass. One study compared the pulsatility index (PI) values between two transit time flowmeters, one manufactured by MediStim ASA and one by Transonic Inc. The EAC noted that one of the studies lay within the manufacturer's search exclusion criteria (data collected prior to cut-off date) but was still included.

The ESC/EACTS guidelines on myocardial revascularisation were used as a reference for the recommended values for the transit time flow measurement

(TTFM) parameters (flow and pulsatility index). This document also recommends graft evaluation before leaving the operating theatre after CABG.

The studies demonstrated that the intra-operative use of the VeriQ transit time flow measurement system in patients undergoing coronary artery bypass graft gives a quantitative assessment of graft patency allowing non optimal grafts to be revised. The VeriQ can also be used as predictor of short term graft failure.

An additional list of 27 studies was submitted by the manufacturer following discussion with NICE and the EAC regarding the small numbers of supporting studies originally presented. 17 of these studies had previously been identified by the EAC in their verification of the manufacturer's search strategy as potentially relevant. The additional evidence included a number of relevant studies which assessed the transit time flowmeter technology using MediStim systems which predated the VeriQ but utilised the same transit time flowmetry principle and therefore were considered to be useful by the EAC.

In the majority of these studies transit time flowmetry is used as a tool for assessing flow in coronary artery bypass grafts. The technique is generally considered a useful method of predicting early graft failure. Criteria for predicting abnormal grafts are proposed in terms of limiting values of measurable parameters. However, one study point out that the measured values can depend on the type and manufacturer of the system and on the system settings. Therefore it is important that both the type of flowmeter and system settings are clearly indicated for graft flow measurements to ensure consistency.

Three further studies identified by the EAC and not included in the manufacturer's additional list of studies were also reviewed. These studies again suggest that transit time flowmetry is a useful tool for assessing flow in coronary artery bypass grafts and in predicting early graft failure.

1.3 *Summary of submitted economic evidence*

The literature searches conducted by the manufacturer identified two economic studies, which were then excluded (by the manufacturer) as not

relevant. The EAC agrees with the exclusion of these studies on the grounds set out in the manufacturer's submission (page 50). However, two of the studies identified by the literature search for clinical effectiveness (Kieser et al (2010) and Becit et al (2007)) were used to provide the data for the cost model. Further data was acquired directly from Dr Kieser in email communications due to her extensive experience in the use of transit time flowmetry systems and from Dr Bergsland in oral communication due to his experience in the use of transit time flowmetry systems and proximity to the manufacturer's associates undertaking the cost analysis.

The cost model estimates the cost savings to the NHS by the introduction of the VeriQ system for the intra-operative assessment of graft patency in all patients undergoing coronary artery bypass grafting (CABG). The savings reported by the manufacturer in the submission of £125.15p are calculated per patient by a bottom-up costing approach. However this figure was found to be incorrect by the EAC. An error appears to have occurred during the data entry for the nurses' wages in the Excel spreadsheet and the wrong value was used for the price of the probe. The correct saving is £121.06p per patient scanned using a PS probe, as calculated by the EAC, with a possible saving to the NHS of £3,389,680 per year if all 28,000 patients (undergoing CABG) are scanned. The time frame covers a period from more then one year (Becit et al (2007)) to up to three years after CABG (Kieser et al (2010)).

The deterministic sensitivity analysis identified the key drivers of the cost analysis to be rate of IABP and rate of MI.

1.4 *Commentary on the robustness of submitted evidence*

1.4.1 Strengths

Clinical evidence

The manufacturer's submission recognises that the main strength in the clinical effectiveness evidence is the fact that none of the studies have been funded by MediStim.

Economic evidence

In general the EAC considered the cost analysis to be adequate in addressing the decision problem. The analysis estimates cost savings from the use of the VeriQ 2011 system in the NHS with a realistic choice of model parameters for realistic clinical scenarios. The rational for the assumption used in the economic assessment seem to the EAC to be reasonable and appropriate. There is a reliance on two papers which are not economic studies but do supply data used in the economic model.

The conclusions of the cost model seem to be supported by the literature and other data sources and shows that the adoption of this technology by the NHS would save the NHS money.

1.4.2 Weaknesses

Clinical evidence

The search for the clinical evidence (by the manufacturer) resulted in 131 records but only four published studies were presented in the manufacturer's submission. Although no additional studies in agreement with the manufacturer's inclusion/exclusion criteria were identified by the EAC, the EAC believes that because the criteria were very strict, a number of relevant studies regarding the use of intra-operative transit time flowmetry in patients undergoing CABG were not included in the clinical evidence. Most of these studies assessed the use of transit time flow measurements with a MediStim device that predated the VeriQ system. However, the EAC believes that the outcomes from these studies could provide evidence for the usefulness of the use of the VeriQ system as it utilises very similar transit time flowmetry technology.

The clinical effectiveness evidence is based on non-randomised data, observational studies and comparisons studies. Studies of such design can potentially introduce bias.

The search strategy used in the identification of the studies is considered appropriate by the EAC. However it is inadequately reported in the manufacturer's submission.

Economic evidence

The searched terms used in the literature search for cost analysis were considered rather generic by the EAC but relevant to the topic under consideration. The two studies identified by the manufacturer's literature search were considered to be irrelevant by the manufacturer and were excluded; the EAC is in agreement with this. The search strategy was not adequately reported in the manufacturer's submission, but the EAC does agree with the strategy used and failed to find any additional relevant studies during its own searches of the literature.

It was noted (by the EAC) that the cost model does not take into account the optional costs of servicing or the time required to undertake training. However, the model is based on one CABG team using the VeriQ for only 220 days per year, if the system is use more frequently the cost per patient scanned would be reduced.

1.4.3 Areas of uncertainty

The EAC is not confident that the inclusion/exclusion criteria were appropriate as they limited the number of included studies submitted by the manufacturer to five for the clinical evidence (four studies and one guidelines document) and none for the economic evidence. Also, it was noted by the EAC that one of the included studies for the clinical evidence lay within the manufacturer's search exclusion criteria. The 27 additional studies submitted by the manufacturer gave useful information on the use of transit time flowmetry on systems which predate the VeriQ (MediStim). Two studies identified in the clinical effectiveness searches were used extensively within the cost model.

1.5 *Key issues*

The manufacturer's submission points out that within the NHS Payment by Results (PbR) funding system 'there are no Diagnostic Related Groups (DRGs) or reimbursement codes for CABG procedures that include a reimbursement for covering the costs of graft patency evaluation that relies on a technology other than Clinical Assessment'. Therefore, potential savings from the use of transit time flowmetry with VeriQ can be made by utilising its potential to annually prevent a certain number of re-operations.

The ESC/EACTS guidelines on myocardial revascularisation recommend graft evaluation before leaving the operating theatre after CABG. This document also provides a reference for the recommended values for the transit time flow measurement (TTFM) parameters. Correct interpretation of flow curves and PI values are important in reducing the number of undetected technical errors and in decreasing the number of grafts erroneously revised.

The manufacturer's submission is based on all 28,000 patient undergoing CABG surgery per year in the NHS being scanned with the VeriQ 2011 using the PS probe. The savings to the NHS could be higher if a proportion of these patients were scanned using the PQ probe (which has a longer life span). Further saving may be possible if only those grafts which are in doubt are scanned and if a VeriQ system was use by more than one CABG team.

2 Background

2.1 *Critique of manufacturer's description of underlying health problem*

The manufacturer's submission outlines the condition for which the technology was considered, as all patients with coronary heart disease who undergo coronary artery bypass grafting (CABG). The manufacturer's submission states that intra-operative assessment of grafts is very important during CABG. The EAC understands that this is included in the scoping document issued by NICE.

Relevant information is provided in relation to the number of CABG operations performed in the UK each year based on information from Coronary Artery Bypass Grafting (2009) Patient UK.

2.2 *Critique of overview of current service provision*

The scope defined by NICE, describes several options for assessment of grafts during CABG.

The manufacturer's submission provides a satisfactory overview of the current service provision in the NHS.

The manufacturer's submission points out that the technology is used intra-operatively for the assessment of flow in new grafts and also to verify graft patency. No guidance has been issued by NICE on intra-operative graft patency verification using transit time flowmetry. The ESC/EACTS have recommended graft evaluation before leaving the operating theatre after coronary artery bypass grafting.

The Clinical Assessment, one of the current practices included in the scoping document, is described in the manufacturer's submission as being the most common method of graft patency verification. The manufacturer's submission points out that the Clinical Assessment does not provide any quantitative data and therefore does not give any information on flow volume or graft quality (page 12 of the manufacturer's submission).

The SPY system (Indocyanine green fluorescence imaging (IFI), Novadaq Technologies) is acknowledged as the second main comparator and the manufacturer states that it can be used complementary to transit time flowmetry with the VeriQ. Other comparators available in the UK market are also reported in the manufacturer's submission.

No evidence is given in the manufacturer's submission about how often transit time flowmetry and the comparators are used in the UK and worldwide.

The main comparator used in the cost analysis section of the manufacturer's submission is Clinical Assessment as specified in the NICE scoping document.

The manufacturer's submission reports that no adverse reactions are related to transit time flowmetry with the VeriQ. The device is certified for direct cardiac use and should only be used by trained surgeons (page 44 of the manufacturer's submission).

The manufacturer's submission suggests that the current clinical pathways should not be affected to a great extent as the device is only used during the CABG procedure and does not significantly affect the length of the procedure.

The manufacturer's submission also states that the VeriQ system will be used mainly by the cardiac surgery teams; therefore no extra staff or extra administration costs will be needed. Training costs will be covered by the supplier/manufacturer (page 14 of the manufacturer's submission). The manufacturer claims that the only cost will be in terms of time needed for the surgical teams to become familiar with the technology and its use.

The manufacturer states that the daily running administration costs are considered to be minimal and should not affect the cost effectiveness of the technology (page 14 of the manufacturer's submission). All data produced by the VeriQ system are stored and can be exported into the patient's electronic notes.

The manufacturer’s submission points out that within the NHS Payment by Results funding system ‘there are no Diagnostic Related Groups (DRG) or reimbursement codes for CABG procedures that include a reimbursement for covering the costs of graft patency evaluation that relies on a technology other than Clinical Assessment’. The manufacturer’s submission underlines that there are no other significant costs related to the technology.

3 Critique of definition of decision problem

3.1 *Patient population*

All patients undergoing coronary artery bypass surgery are considered as being relevant in the scoping document issued by NICE. The manufacturer's submission focuses on this population (28,000 per year). No subgroups were defined in the NICE scoping document.

3.1.1 Intervention

The intervention considered in the manufacturer's submission is the VeriQ which is a non-invasive, real time ultrasound system used during surgery to assess graft flow. The manufacturer provides three versions of the device; the system considered in the VeriQ 2011 with the PS probe.

The manufacturer states that the VeriQ system incorporates several ultrasound modalities and therefore can be used for a range of surgical interventions in addition to graft flow assessment. The system utilises the established technology of transit time flow measurements to measure blood flow in veins and arteries intra-operatively. The manufacturer states that the VeriQ 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'.

A description of the VeriQ system is not given in the manufacturer's submission, the following is taken from information on the manufacturer's website.

The VeriQ measures blood flow with sterile probes and a real time flow curve is displayed together with mean flow (ml/min), pulsatility index (PI) and diastolic filling percentage (DF%). The system consists of a computer system with a 160 GB hard drive and a 19 inch touch screen mounted on a trolley. To assist the surgeon during the planning of grafting procedures or as an addition to the flow measurement, the VeriQ system can provide ultrasound imaging with a high frequency, sterilisable ultrasound probe. Using other probes, it is also possible to measure velocity with Doppler.

The manufacturer's submission states that the VeriQ system has been CE marked (received 2003 no. EU0211003) and is described in the EU certificate as a 'medical ultrasonic non-imaging flow meter system' (page 5 of the manufacturer's submission). Details of approval outside the UK are also provided (page 7 of the manufacturer's submission).

The manufacturer's submission states that the device is certified for direct cardiac use and should only be used by trained surgeons (page 44 of the manufacturer's submission). It is considered to be very safe and presents no threat to users or patients. No protective equipment is required for its use.

3.1.2 Comparators

The possible comparators for the VeriQ system are identified in the NICE scoping document as Clinical Assessment of graft flow, the SPY system (Indocyanine green fluorescence imaging (IFI), Novadaq Technologies), Electromagnetic flow meters, Intra-operative or completion Doppler (auscultation), Intra-operative or completion Duplex imaging and Intra-operative or completion angiogram. However, the manufacturer's submission identifies Clinical Assessment and SPY Indocyanine green fluorescence imaging as the main comparators on the basis that these are the techniques mostly used today in the UK and that there are not enough data comparing VeriQ transit time flow measurements to any of the other comparators.

It should be noted that post-operative angiography is generally considered to be the 'gold standard' for anatomic evaluation.

This comparator choice is consistent with the scoping document, although it may be useful to consider further comparators in order to investigate additional options.

The NICE scoping document states that for the purposes of the cost analysis the most relevant UK comparator is considered to be Clinical Assessment of graft flow.

3.1.3 Outcomes

The outcomes included in the manufacturer's submission are consistent with the NICE scoping document. The clinical outcome measures considered in the manufacturer's submission include peri- and post-operative clinical events associated with graft failure (including mortality) and long term morbidity and mortality. The system related outcomes include assessment of the values of the transit time flowmetry parameters.

Some additional system-related outcome measures were featured in the NICE scoping document, such as 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. These were not considered in the manufacturer's submission as they were not assessed in any of the five included studies (four studies and one guidelines document) for the clinical evidence.

No safety outcomes or adverse events related to transit time flowmetry with the VeriQ are reported.

3.2 *Time frame*

The cost analysis provided in of section 6 (6.3.7) of the manufacturer's submission states the cost and clinical outcomes occur either peri-operatively or over a period of one to three years.

3.3 *Other relevant factors*

The manufacturer's submission acknowledges that the interpretation of data requires one half day of theoretical training plus some training time during a few CAGB procedures for the operator to become proficient in the use and interpretation of the data presented by the VeriQ system. The manufacturer states that training will be provided free of charge.

3.4 *Equality and diversity issues*

No equality and diversity issues are identified to be addressed in the manufacturer's submission for the use of the VeriQ system. The VeriQ is suitable for use of all patients irrespective of age, gender or ethnicity.

4 Clinical effectiveness

4.1 *Critique of manufacturer's approach*

4.1.1 Description and critique of the manufacturer's identification and selection of studies.

Assessment of literature searches

The VeriQ system is used for the intra-operative, non-invasive assessment of graft flow during coronary artery bypass surgery. The manufacturer's submission presents evidence for the effectiveness of intra-operative transit time flow measurement with the VeriQ system for the assessment of graft patency during coronary artery bypass grafting (CABG) and in predicting short and medium-term outcomes.

The manufacturer's submission states that literature searches were undertaken in all the databases suggested by NICE which included Embase, Medline, Medline (R) In Progress and The Cochrane Library. However, only one search strategy is presented in Appendix 2, section 7.2.4 (page 91 of the manufacturer's submission). The EAC contacted the manufacturer and was informed that the reported search strategy was performed in Pubmed (which incorporates Medline and Medline (R) In Progress). The searches were then replicated in the other databases to identify any additional studies. The EAC was also presented with some additional information regarding the number of hits in each searched term for the Pubmed search. However, there is no information in the manufacturer's submission report on the number of studies identified in the other databases. The EAC considers that it would have been much more appropriate if separate searches and different strategies were undertaken and then presented in the manufacturer's submission document for each separate database.

The EAC noted that the Pubmed search strategy was not sensitive. The terms used in the search strategy were considered to be appropriate but the EAC noticed the absence of the use of any subject index headings (for example MeSH), synonyms, wildcards or truncation which increases the likelihood of relevant studies being omitted from the search.

The search date span is limited to the last 8 years (2004 to 2011) which is appropriate as the VeriQ system was launched in 2004 and CE marking was received in 2003.

There is no indication that any other limits were applied in the search strategy.

Using the search strategy in Pubmed shown in Appendix 2 of the manufacturer's submission, the EAC identified 138 studies and a small number of additional papers were identified when Embase was searched (section 6 of this report).

The manufacturer's submission also states that '*additional searches'* were performed in the manufacturer's own database of published studies. No further information is reported in the manufacturer's submission regarding those searches. Consequently, it is unclear in the manufacturer's submission which studies were identified following the searches in the databases and which were identified in the manufacturer's own database.

In total 131 studies were identified.

The searches for evidence on '*adverse events'* were reported in Appendix 4, section 7.4 (page 102 to 103 of the manufacturer's submission). The terms used for this search are reported in the manufacturer's submission but without the details of the complete search strategy. As there is no indication of which database was searched, the EAC assumed that the same databases as for the clinical evidence were searched.

The manufacturer's submission states that no studies with adverse events were identified. It also states that adverse events regarding the VeriQ system are reported directly to the manufacturer, as Health Institutions are obliged to report any adverse event with intra-operative devices directly to the manufacturer. No known adverse reactions have been recorded in their own database related to the transit time flowmetry with the VeriQ system.

Use of inclusion/exclusion criteria in the selection of studies

The inclusion criteria used for the selection of studies in the manufacturer's submission table B1 (page 21 of the manufacturer's submission) are consistent with the decision problem and therefore are considered to be appropriate. Patients included were those undergoing coronary artery bypass surgery, and the technology eligible for inclusion was the VeriQ system or any transit time flow measurement system manufactured by MediStim. Studies included were published studies based on data collection after the VeriQ launch in 2004. The included outcomes were any benefit or effect of the VeriQ on the outcome of the CABG surgery. Some of the system related outcomes specified in the scoping document were not featured in the inclusion criteria.

The exclusion criteria used for the selection of studies were quite strict and the EAC understands that a number of relevant studies are excluded. Studies where a MediStim transit time flow measurement device that predated 2004 was used or studies referring to the use of non MediStim transit time flowmetry technology (unless as a comparator) as well as studies where transit time flowmetry was used as a control method to compare surgical techniques were excluded. Studies in any language other than English were also excluded. Study designs comprising case studies, reviews and editorials were not included in the selected studies.

In total the clinical effectiveness search identified 131 references of which 15 (studies 1 to 15) were considered relevant. However, no data abstraction strategy is reported in the manufacturer's submission and therefore the EAC has no information how the number of relevant studies was limited to 15. The full list of the 15 studies is presented in Table B2 (page 23) in the manufacturer's submission and Appendix 1 of this report

The list is completed with some information on each study. However, the EAC noticed that the reference of study 9 (Leacche et al. (2009)) is not the correct one. Also the number of grafts in study 3 (Becit et al. (2007)) is half of what is reported.

The EAC would also like to point out the use of the word 'intervention' in the manufacturer's submission where it seems to be synonymous with the

‘surgical procedure’, whereas in the NICE documents it is ‘the technology under assessment’.

Of the 15 studies considered for the review, 5 were identified as being relevant and 10 were excluded and are shown in Tables 1 and 2 of this report respectively.

4.1.2 Table of identified studies - studies included in and excluded from the submission

Included studies

Five studies, made up of four clinical effectiveness studies and one guidelines document, were identified as being relevant in the manufacturer’s submission. These studies are presented in Table 1.

None of the included studies was a RCT. Two of the studies (2 and 3) were retrospective cohort observations studies, one (study 14) was a prospective analysis and one (study 12) was a comparative study. Study 15 was the European guidelines on myocardial revascularisation therefore was not included in the critical appraisal completed by the manufacturer.

There was no difference between patient groups for each study. None of the studies was gender specific and all were conducted in different hospitals in Europe and Canada but none in the UK.

The duration of the follow up varied from 6 weeks to 6 months.

Two studies (2 and 3) evaluated transit time flowmetry with the use of the VeriQ system in assessing graft patency compared to Clinical Assessment. One study (12) was a comparative assessment of the Pulsatility Index as calculated by two transit time flowmeters from MediStim ASA and from Transonic Inc. Study 14 investigated the predictive values of transit time flowmetry in CABG with regard to short-term graft patency and long-term patient survival.

None of the studies included in the manufacturer’s submission was funded by the manufacturer MediStim ASA or by any other manufacturer.

Table 1. Included studies from manufacturer's submission

Study no	Intervention	Comparator	Title	Ref
Study 2 Kieser et al.	CABG	Clinical Assessment	Transit-time flow predicts outcomes in coronary artery bypass graft patients: a series of 1000 consecutive arterial grafts.	*European Journal of Cardiothoracic Surgery*. 38, 155-162, 2010.
Study 3 Becit et al.	CABG	Clinical Assessment	The impact of intra-operative transit time flow measurements on the results of on-pump coronary surgery	*European Journal of Cardiothoracic Surgery*. 32, 313-318, 2007.
Study 12 Nordgaard et al.	CABG	Transonic Inc transit time flowmetry system	Pulsatility index variations using two different transit-time flowmeters in coronary artery bypass surgery	*European Journal of Cardiothoracic Surgery*. 37, 1063-67, 2010.
Study 14 Jokinen et al.	CABG	PCI	Clinical value of intra-operative transit-time flow measurement for coronary artery bypass grafting: a prospective angiography controlled study	*European Journal of Cardiothoracic Surgery*. In press, corrected proof available online, 20 November 2010.
Study 15 ESC/EACTS.	CABG	N/A	Guidelines on myocardial revascularisation	*European Heart Journal*. 31, 2501-2555, 2010 (paragraph 10.2.2)

EAC summaries of included studies

Study 2. Kieser et al. (2010). The authors evaluated transit time flow measurement (understood to be a VeriQ system (MediStim) from manufacturer although not stated in the paper) as a tool to intra-operatively detect technical errors in coronary artery bypass grafting and predict outcomes. 336 consecutive CABG patients with a total of 1000 arterial grafts were assessed with transit time flowmetry. 20 grafts (2%) were revised. It was concluded that a high pulsatility index value (>5) predicts a technically inadequate arterial graft during surgery and also predicts early post-operative adverse events, particularly mortality, even if all other intra-operative assessments indicate good graft quality.

Study 3. Becit et al. (2007). The effect of the detection of graft dysfunction by intra-operative transit time flow measurements (VeriQ1101 (MediStim)) on surgical results of on-pump CABG in a retrospective cohort study was evaluated. The study comprised two series of 100 consecutive patients; Group A was not submitted to intra-operative transit time flow measurement and Group B was submitted to intra-operative transit time flow measurement. Graft revision was performed with pusatility index (PI) >5 and backward flow

(BF) <50%. The authors reported that 3% of total grafts in 9% of patients were revised with a significant reduction in morbidity and mortality in the transit time flow measurement group compared with the no-transit time flow measurement group.

Study 12. Nordgaard et al. (2010). Transit time flow measurements are widely accepted as an intra-operative method of assessing coronary artery bypass grafting. The two most used flowmeters, manufactured by MediStim (VeriQ) and Transonic, have different default filter settings of 20 Hz and 40 Hz respectively. This may cause differences in the flow measurement which could influence the reported results. The aim of the study was to compare the pulsatility index values recorded by each system in two different clinical settings: analysis of flow patterns recorded simultaneously by both flowmeters in the same coronary artery bypass grafting procedure (19 cases) and evaluation of flow patterns under different levels of filter setting (5, 10, 20, 30, 50 and 100 Hz) in the same grafts (8 cases). If was found that the Transonic device provided substantially lower pulsatility indexes when compared to the MediStim VeriQ device. Also, by increasing the filter setting in the flowmeter, the pusatility index (on both systems) increased considerably. The authors concluded that the Transonic flowmeter displayed a lower pulsatility index than the MediStim VeriQ system due to the lower default filter setting. Also, as different filter settings show different pulsatility indexes, care must be taken when flow values and flowmeters are compared. Ideally, the type of flowmeter should be clearly indicated whenever graft flow measurements and derived indexes are provided to ensure consistency.

Study 14. Jokinen et al. (2010). The predictive value of transit time flowmetry (MediStim, likely to be an earlier system that the VeriQ as the data were collected prior to 2004) was assessed post-operatively in 75 elective CABG patients with a total of 204 grafts, with regard to short-term graft patency and long-term patient survival. Graft patency was assessed using coronary angiography 199±42 days following the operation. The authors concluded that transit time flowmetry can predict graft failure within six months after CABG but does not predict long-term outcome. The EAC noticed that this study was

based on data collected before 2004 and even though this was confirmed in the manufacturer's submission (page 39) the study was not excluded.

Study 15. ESC/EACTS Guidelines on myocardial revascularisation. (2010). The ESC/EACTS task force on myocardial revascularisation produced the ESC/EACTS guidelines on myocardial revascularisation (2010) and recommended graft evaluation before leaving the operating theatre after CABG. Graft flow measurement, related to graft type, vessel size, degree of stenosis, quality of anastomosis and outflow area is useful at the end of surgery. A flow <20mL/min and pulsatility index >5 predict technically inadequate grafts, mandating graft revision before leaving the operating theatre.

Conclusions. Transit time flowmetry is considered to be valuable tool for predicting early graft failure in CABG patients with the ability of improving surgical results. Criteria for predicting abnormal grafts in terms of limiting values of parameters such as pulsatility index (PI) are proposed. However, the measured values can depend on the type and manufacturer of the system and on the system settings. Therefore it is important that both the type of flowmeter and system settings are clearly indicated for graft flow measurements to ensure consistency.

Excluded studies

Details of the studies that were excluded from the manufacturer's submission and the reasons behind the exclusions were provided in the submission document (section 5.2.4, pages 25-27 of the manufacturer's submission). The reasoning for the exclusion was considered by the EAC as being consistent with the exclusion criteria set by the manufacturer in the majority of the excluded studies.

However, study 11 (Kim et al (2010)) was excluded due to the collection of data starting before 2004. This was in agreement with the manufacturer's submission exclusion criteria but the EAC noticed that one of the included studies (Jokinen et al (2010)) was also based on data collected before 2004

and even though this was acknowledged in the manufacturer's submission (page 39) the study was not excluded.

Table 2. Excluded studies from manufacturer's submission

Study no	Intervention	Comparator	Title	Ref
Study 1 Mack.	CABG	Intra-operative fluorescence imaging, intra-operative angiography, epicardial echocardiography, TOE, thermal coronary angiography.	Intra-operative coronary graft assessment	*Current Opinion in Cardiology*. 23(6), 568-72, Nov 2008.
Study 4 Jalal.	CABG	N/A	An objective method for grading of distal disease in the grafted coronary arteries	*Interactive CardioVascular and Thoracic Surgery* 6, 451-455, 2007.
Study 5 Nordgaard et al.	CABG	High-frequency epicardial ultrasound	Different graft flow patterns due to competitive flow or stenosis in the coronary anastomosis assessed by transit-time flowmetry in a porcine model	*European Journal of Cardiothoracic Surgery*. 36, 137-142, 2009.
Study 6 Trachiotis.	CABG	N/A	Letter to the editor - Value of diastolic flow with transit-time flow meters in coronary artery bypass surgery	*European Journal of Cardiothoracic Surgery*. 39, 431, 2011.
Study 7 Nordgaard et al	CABG	N/A	Reply to above letter to the Editor	*European Journal of Cardiothoracic Surgery*. 39, 431, 2011.
Study 8 Colli et al.	CABG	Post Operative Angiography	Routine intra-operative completion Angiography after coronary artery bypass grafting or routine intra-operative transit time flow measurement to check graft's quality?	*Journal of the American College of Cardiology*. 54, 2337-2338, 2009.
Study 9 Leacche et al.	CABG	Intra-operative fluorescence imaging (IFI) (SPY; Novadaq Technologies), High-frequency epicardial ultrasound	Intra-operative Grafts Assessment	*Seminars in Thoracic and Cardiovascular Surgery*. 21, 207-212, 2009.
Study 10 Singh et al.	CABG	Indocyanine green (ICG) fluoroscopy (SPY, Novadaq Technologies)	The graft imaging to improve patency (GRIIP) clinical trial results	*Journal of Thoracic and Cardiovascular Surgery*. 139, 294-301, Feb 2010.
Study 11 Kim et al.	CABG	Early post-operative angiography	Ten-year experience with off-pump coronary artery bypass grafting: Lessons learned from early post-operative angiography	*Journal of Thoracic and Cardiovascular Surgery*. 139, 256-262, 2010.
Study 13 Hatada et al.	CABG	Intra-operative fluorescence imaging (IFI) (SPY; Novadaq Technologies, Inc, Toronto, Canada)	Comparison of the waveforms of transit-time flowmetry and intra-operative fluorescence imaging for assessing coronary artery bypass graft patency	*General Thoracic and Cardiovascular Surgery*. 59(1), 14-18, 2011, Epub 12 Jan 2011.

No relevant '*ongoing'* studies were identified by the manufacturer.

Four of the excluded studies (studies 1, 4, 5 and 13) were included in the additional list of 27 studies presented by the manufacturer at a later date at the request of NICE and the EAC (section 4.3 of this report).

Details of relevant studies that were not included in the submission

1. The EAC re-ran the manufacturer search in Pubmed; 138 references were identified. (section 6 of this report)

2. The EAC ran searches in other databases recommended by NICE replicating the manufacturers search strategy.

   EAC Cochrane Library search: The search returned 48 references (accessed 03/03/11).

   EAC Embase search: The search returned 149 references (accessed 03/03/11)

Three further studies relevant to the use of the VeriQ were identified by the EAC (see section 4.4 and appendix 3 of this report).

4.1.3 Description and critique of manufacturer's approach to validity assessment and details of the quality assessment of studies

A critical appraisal of all of the identified studies was undertaken by the manufacturer and reported in Appendix 3 of the manufacturer's submission (section 7.3, pages 93 to 102). The manufacturer assessed the quality of the clinical effectiveness studies using appropriate criteria. Four of the five studies included in the manufacturer's submission were assessed. Study 15 was the ESC/EACTS guidelines on myocardial revascularisation and therefore was not critically appraised by the manufacturer.

It is not clear whether the studies were assessed by a single reviewer or multiple reviewers. The manufacturer's comments regarding the studies' approach to addressing the areas covered by the question can be seen in Table 3 with additional comments by the EAC.

Table 3. Manufacturer's assessment of included studies

Kieser et al. (2010).

Transit-time flow predicts outcomes in coronary artery bypass graft patients: a series of 1000 consecutive arterial grafts. *European Journal of Cardiothoracic Surgery.* 38, 155-162, 2010.

In this study, TTF was used in 336 consecutive patients to assess the value of this method in predicting post-operative major adverse cardiac events (MACEs). Their findings suggest that the pulsatility index (PI), one of three TTF measurements, is highly predictive of outcomes. (**EAC note:** It is understood from the manufacturer that the VeriQ system was used for this study).

Study question	**How is the question addressed in the study?**	**Comments by EAC**
Was randomisation carried out appropriately?	The study is a retrospective analysis of data from consecutive patients of a single surgeon. There was no randomisation 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).	The trial was not randomised.
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 intra-operatively.	EAC in agreement.
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.	EAC in agreement.
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.	EAC in agreement.
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.	EAC in agreement.
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.	EAC in agreement.
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.	EAC in agreement.

Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination

Becit et al. (2007).

The impact of intra-operative transit time flow measurement on the results of on-pump coronary surgery. *European Journal of CardioThoracic Surgery.* 32, 313-318, 2007.

The purpose of the study was to evaluate the effect of detection of graft dysfunction by intra-operative TTFM on the surgical results of on-pump CABG**.**

Study question	**How is the question addressed in the study?**	**Comments by EAC**
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).	Retrospective cohort study (level 2b)
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, smoking, arterial hypertension, 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).	There was no significant difference in patient data between the two groups
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.	EAC in agreement.
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 intra-operatively, and not over an extended period of time, it is difficult for patients to drop out or be excluded from the study data.	EAC in agreement.
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.	EAC in agreement.
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.	EAC in agreement.

Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination

Jokinen et al. (2010).

Clinical value of intra-operative transit-time flow measurement for coronary artery bypass grafting: a prospective angiography-controlled study. *European Journal of Cardiothoracic Surgery,* In press, corrected proof available on-line, 20 Nov 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. (**EAC note:** It is unlikely that the VeriQ system was used as the data were collected prior to 2004).

Study question	**How is the question addressed in the study?**	**Comments by EAC**
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.	EAC in agreement.
Was the concealment of treatment allocation adequate?	All patients / grafts treated (APT): CABG and TTMF.	EAC in agreement.
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'	EAC in agreement.
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	EAC in agreement.
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.	EAC in agreement.
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.	EAC in agreement.
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.	EAC in agreement.

Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination

Nordgaard et al. (2010).

Pulsatility index variations using two different transit-time flowmeters in coronary artery bypass surgery. *European Journal of Cardiothoracic Surgery*. 37, 1063-1067, 2010.

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. (**EAC note:** A MediStim system, understood from the manufacturer to be a VeriQ, and a system from Transonoic were used for this study).

Study question	**How is the question addressed in the study?**	**Comments by EAC**
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.	Comparative study
Was the concealment of treatment allocation adequate?	Treatment allocation equal for all 10 patients operated on by the same surgeon.	EAC in agreement.
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.	EAC in agreement.
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	EAC in agreement.
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	EAC in agreement.
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.	EAC in agreement.
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) analysed measured	EAC in agreement.
Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

4.1.4 Description and critique of manufacturer's outcome selection

The included studies looked at post-operative outcomes and how the use of the VeriQ system can predict these outcomes or justify intra-operative graft revision.

The primary outcomes that were investigated in the included studies were the assessment of the value of the transit time flowmetry in predicting short-term graft patency, per/post-operative clinical events associated with graft failure (infarction and mortality). In one study the primary outcome was system related as the VeriQ was compared to another similar technology. For most of the studies no secondary outcomes were reported.

All these outcomes were addressed in the scoping document issued by NICE. Although additional system-related outcomes (number of probes per procedure, time to generate data, etc) are featured in the scoping document (page 18 of the manufacturer's submission) they were not addressed by the manufacturer. The EAC acknowledges that there was no information on these topics in the included papers.

4.1.5 Description and critique of the statistical approach used

The statistical analyses presented within the included research studies were adequately reported by the manufacturer. The primary hypothesis, the sample size and the statistical analyses used for testing the hypothesis were reported in the manufacturer's submission.

A two-sided p-value of <0.05 was used in all of the included clinical studies to indicate statistical significance.

In the Kieser et al. (2010) study Fisher's test was used to compare data and a univariate logistic regression analysis was done for each of the potential predictor variables of MACE. In the Becit et al. (2007) study the independent two-sample t-test and Fisher's chi-squared test were used to compare the two groups. In Nordgaard et al. (2010) sample tests and a Wilcoxon test were used to compare flow assessments. Jokinen et al. (2010) analysed their data using a non-parametric Mann-Whitney U-test and Kaplan-Meter's survival

analysis. The correlation between the measured flow values and graft patency was described with Spearman's rank test.

All patients who were included in the studies were defined as being CABG patients. No patients were dropped out or excluded from the study data.

No additional statistical analysis was undertaken by the manufacturer. Meta-analysis was not provided on the grounds that it was inappropriate. The EAC agrees that meta-analysis was not feasible.

4.1.6 Summary statement about the review of clinical effectiveness

The studies included in the manufacturer's submission are relevant to the decision problem, in terms of patient populations and interventions, and the submitted evidence adequately reflects the decision problem. The relevant data from the included studies have been reported in the manufacturer's submission document.

Additional searches carried out by the EAC, including re-running the manufacturer's search strategy, even though a slightly larger number of relevant studies were identified, did not find additional relevant studies in agreement with the inclusion/exclusion criteria.

The manufacturer's submission included validation and quality assessment of the included research studies. The validity assessment was adequate, although there was no information on the number of reviewers. The clinical outcomes selected for the assessment of the VeriQ system relate to those outlined in the NICE scoping document and the statistical methods undertaken by the included studies were adequately and appropriate reported.

4.2 *Summary of submitted evidence*

The evidence submitted by the manufacturer comprised four observational studies from different hospitals in Europe and Canada as outlined in section 4.1.2 of this report. The findings from these studies presented in the manufacturer's submission and also from the EAC review of the papers, are summarised below.

4.2.1 Summary of results

Results from the included studies are presented (pages 37 to 41 of the manufacturer's submission). The results are consistent with the evidence provided in the studies.

Transit time flow for predicting short-term outcomes in CABG

Three studies evaluated the effect of transit time flow in detecting graft dysfunction and predicting outcomes in patients undergoing CABG.

The Kieser et al. (2010) study measured and assessed the three parameters in transit time flowmetry; pulsatility index (PI), flow and diastolic filling (DF) in 990/1000 arterial grafts in 336 patients. The results showed that a pulsatility index value >5 is a predictor for the occurrence of future MACE ($p = 0.005$) and mortality following non-emergent surgery ($p = 0.02$). Flow and diastolic filling were not predictive of outcomes.

The Becit et al. (2007) study reviewed the grafts in two groups of patients. A statistically significant reduction ($p < 0.05$) in the rate of the overall morbidity (from 16% to 6%), IABP insertion, peri or post-operative infarction (from 5% to 0%) and mortality (from 4% to 0%) was found in the group in which the transit time flowmetry was routinely performed intra-operatively for the assessment of graft patency.

Jokinen et al. (2010) concluded that transit time flowmetry predicts graft failure within 6 months but it does not predict long-term outcome.

System related results

Nordgaard et al. (2010) demonstrated that the VeriQ system gives higher pulsatility index values compared to the Transonic system ($p < 0.001$) due to the different default settings.

Guidelines and recommendations

The ESC/EACTS guidelines on myocardial revascularisation (2010) recommended graft evaluation before leaving the operating theatre after

CABG. Graft flow measurement is useful at the end of surgery, a flow <20mL/min and pulsatility index >5 predict technically inadequate grafts, suggesting graft revision before leaving the operating theatre.

Adverse events

There is no published evidence for adverse events associated with the use of the VeriQ system.

4.2.2 Critique of submitted evidence syntheses

The manufacturer's submission did not undertake any meta-analysis. The studies included in the manufacturer's submission did not feature any randomised controlled trials and the EAC agrees any meta-analysis would not be worthwhile due to the limited number of studies and differences in patient populations.

The manufacturer's submission provides a summary of clinical findings in relation to transit time flow measurements with the VeriQ and graft patency and MACE from all the included studies.

4.3 *Additional studies submitted by the manufacturer*

Following discussion with NICE and the EAC regarding the small numbers of supporting studies originally submitted, an additional list of studies was presented by the manufacturer (Appendix 2 of this report). The additional evidence included a number of relevant studies which assessed the transit time flowmeter technology using MediStim systems which predated the VeriQ. These systems included CardioMed (CM) and Butterfly Flowmeter (BF) ranges. Both these devices utilise the same transit time flowmetry principle as the VeriQ (with some differences in the hardware and software) and therefore were considered to be useful by the EAC. Thus the additional studies should aid in determining the value of transit time flowmetry in clinical practice and any effect on current clinical pathways.

No search strategy was reported in the manufacturer's submission for the additional studies. The EAC understood that these studies were identified from the original search.

The additional list included 27 studies and was presented by the manufacturer in a tabulated form with some information about each study (the list is of studies is shown in Appendix 2 of this report). Two of these studies (Study 2 - Jokinen et al. (2010) and Study 8 - Nordgaard et al. (2010)) were already included in the four studies and one guidelines document originally submitted as part of the clinical effectiveness evidence and have been reviewed earlier in this report (section 4.1.2). Of the remaining 25 studies, four (studies 3, 4, 5 and 6) were from the list of studies previously excluded by the manufacturer (table 2 of this report). Most of the studies (20 CABG studies, one lower limb study (study 26) and one animal study (study 5)) were retrospective cohort studies covering a range of cohort sizes and comparators, two were reviews (studies 3 and 16) and one was a case report (study 7).

Excluding the two studies previously reviewed (studies 2 and 8), 23 of the studies (including both of the reviews and the lower limb study) use MediStim transit time flowmetry systems which predate the VeriQ (Butterfly Flowmeter (BF) or CardioMed (CM) ranges) but operate on similar principles. The EAC therefore considers these studies to be useful in providing general evidence for the use of MediStim transit time flowmeter systems for graft assessment. One study (study 5, the animal study) uses a transit time system from another manufacturer (GE), the instrumentation used is not stated in one study (study 4). Considering the two reviews, one study compares a MediStim instrument with a Transonic device and one study reviews a range of techniques and instrumentation (including a MediStim instrument) for graft assessment.

Each study was reviewed and summarised by the EAC.

1. **Beran et al. (2010).** This study aimed to analyse the predictive value of intra-operative bypass graft flow measurements on long term mortality. A total of 1593 patients undergoing coronary artery bypass graft procedures underwent intra-operative bypass graft flow measurements using a transit time flow meter (CardioMed (MediStim)). The pre-operative left ventricular ejection fraction was also measured using echocardiography. The follow-up time varied between 0.5 and 8.8 years (mean 3.7 years), overall mortality was 10.1%. The authors concluded that the pre-operative left

ventricular ejection fraction was the highest independent predictor of long-term survival. However, transit time flow measurements were considered to be a useful tool in performing surgical quality control and in identifying anastomotic problems at an early stage to prevent harm to the patient. This technique was considered less time consuming and less invasive than other methods such as immediately post-operatively performed coronary angiography.

2. **Jokinen et al. (2010).** *Study in original manufacturer's submission (see section 4.1.2 of this report).*

3. **Mack M.J. (2008).** In this review paper the authors suggest that intra-operative graft assessment in coronary artery bypass grafting is not frequently performed. However, a review of previous studies showed that graft occlusion occurs frequently after coronary artery bypass grafting with an immediate graft closure rate of 5% to 9% and a one year closure rate of 20% to 30%. Coronary angiography is the accepted standard for graft assessment but is seldom employed due to logistical problems and image quality. Two other methods, transit time flow measurement (Transonic and MediStim) and intra-operative fluorescence imaging are considered as simple, safe and expeditious and have been shown to be predictive of graft failure. Transit time flow measurements provide an objective measurement of graft flow but do not provide a visual image of the graft and may be more sensitive to other factors that may cause the technique to either underestimate or overestimate the need for graft revision. However, wider use of this technique may reduce graft failure although intra-operative coronary angiography remains the gold standard option for immediate graft assessment.

4. **Jalal A. (2007).** In this 'work in progress' report the author suggests that the impact of the diffuseness of coronary artery disease on the outcome of coronary bypass grafting was unclear due to the absence of an objective grading system. The study proposed a grading system (0 to 3 with increasing severity) and validated it by transit time flow measurements. The graft flow was measured and the pulsatility index calculated for a

range of vessels in 186 patients. It was concluded that the proposed method of grading provided an objective and reliable system for the assessment of the severity of distal disease in grafted coronary arteries.

5. **Nordgaard et al. (2009).** The objective of this animal study was to assess whether coronary graft flow patterns were affected differently by native coronary competitive flow or by stenosis of the coronary anastomosis. Nine pigs underwent off-pump grafting of the left internal mammary artery to the left anterior descending artery. Flow patterns in the mammary grafts were recorded using ultrasound (Vivid 7 scanner (GE)) under a range of conditions: baseline flow, full competitive flow, partial competitive flow and after creation of a stenosis in the anastomosis. Competitive flow was achieved by an adjustable occluder in the left anterior descending artery. Mean flow values during different flow conditions (diastole, systole, etc) were calculated as a ratio of the baseline value and compared to each other. A number of flow indexes were derived and calculated and compared in the same manner. The results showed that mammary graft flow was significantly reduced by native coronary competitive flow but marginally decreased by a stenotic anastomosis. Reduction of graft flow was particularly evident in the diastole.

6. **Hatada et al. (2011).** A prospective comparison of the diagnostic accuracy of fast Fourier transformation analysis of the transit time flowmetry waveform (BF1000 (MediStim)) and intra-operative fluorescence imaging (SPY (Novadaq Technologies)) to determine graft failure was carried out. Saphenous vein grafts on six patients (ten grafts) were evaluated intra-operatively with both transit time flowmetry and intra-operative fluorescence imaging. The patients also underwent post-operative X-ray angiography. Mean graft flow and pulsatility index were calculated from the transit time flowmetry measurements and the waveforms were analysed to provide the harmonic distortion. The authors concluded that the harmonic distortion of the transit time flowmetry waveform can provide better diagnostic accuracy for detecting the quality of grafts than either the mean graft flow or pulsatility index or the use of intra-operative fluorescence

imaging. However, as this was a pilot study, it was suggested that the number of patients examined by both systems should be increased.

7. **Economopoulos et al. (2010).** A single case is reported where a subclavian artery stenosis was suspected based on measured parameters from transit time flowmetry (BF2000 (MediStim)) such as poor flow, high pulsatility index and almost zero mean flow. Post-operative CT angiographic evaluation demonstrated a severely calcified stenotic lesion in the proximal left subclavian artery.

8. **Nordgaard et al. (2010)** *Study in original manufacturer's submission (see section 4.1.2 of this report).*

9. **Takami et al. (2009).** The flow characteristics of right gastroepiploic arterial grafts, frequently used in coronary artery bypass grafting were investigated using intra-operative transit time flowmetry (BF2000 (MediStim)). A range of flow parameters were measured in 111 patients who also underwent post-operative X-ray angiography. The authors concluded that intra-operative transit time flow profiles of the functional in situ gastroepiploic arterial grafts were variable and could be classified in four types closely associated to the disease severity of the target coronary artery. The findings may help surgeons to judge the anastomosis quality of grafts in the operating room.

10. **Nordgaard et al. (2009).** The mean flow and pulsatility index of sequential saphenous vein grafts was evaluated in 1390 grafts (in 581 patients) using transit time flowmetry (MediStim). The results showed significant differences ($p<0.001$) in flow and pulsatility index measured in single or sequential vein grafts. It was concluded that blood flow increases from single to double and up to triple sequential grafts and the pulsatility index of the right coronary system is significantly higher than that of grafts to the left coronary system.

11. **Weber A, Tavakoli R and Genoni M. (2009).**The purpose of this study was to examine the advantages of the use of the internal thoracic artery over that of the saphenous vein for revascularisation of the circumflex or

right coronary artery. Intra-operative flow measurements were carried out using a Medistim BF2004 system on 306 patients undergoing off-pump coronary artery bypass grafting. The results showed that the internal thoracic artery provided superior flow properties than the saphenous vein to the circumflex or right coronary artery areas with reduced peri-operative ischemia. However, further investigation was required to assess whether this advantage persisted after adjusting for the grade of the proximal coronary stenosis.

12. **Tokuda et al. (2008).** The ability of transit time flowmetry to predict midterm graft failure was assessed in this retrospective cohort study. Post-operative angiography was performed at between one and four years after surgery in 104 grafts (in 51 patients), which had been evaluated by transit time flowmetry (BF1001 (MediStim)) and confirmed to be fully patent in early post-operative angiography. It was concluded that transit time flowmetry provides a good prognostic index for both early and midterm follow-up.

13. **Herman et al. (2008).** The authors used transit time flowmetry as this technique enables immediate intra-operative assessment of blood flow parameters in coronary artery bypass grafts (CABG). The graft patency in 985 CABG patients was assessed using a transit time flowmeter (Butterfly Flowmeter (MediStim)) in this retrospective cohort study. Nearly 1% of the patients were shown to have abnormal flow which prompted surgical graft revision. The study further examined the predictive value of measured graft flows on early and medium-term outcomes. The findings suggested that abnormal flows measured intra-operatively are independently associated with short-term in-hospital outcome.

14. **Balacumaraswami et al. (2008).** In this observational study prospectively recorded intra-operative flow measurements on series of 266 grafts in 100 CABG patients undergoing both off-pump (203 grafts, 80 patients) and on-pump (63 grafts, 20 patients) surgery were investigated using transit time flowmetry (BF2004 (MediStim)). The study demonstrated that the mean graft flow and flow/pressure ratio were significantly higher and the mean

arterial pressure significantly lower for all grafts in the on-pump group. There was no difference in the mean graft flow and flow/pressure ratio of arterial grafts, which were significantly less than for long saphenous vein grafts. In patients with unstable angina and/or hemodynamic instability, there is a possibility of a lower graft flow in arterial grafts and therefore off-pump surgery should be considered. The authors support the need to assess intra-operative graft flow in order to detect and correct graft failure.

15. **Tokuda et al. (2007).** In this retrospective cohort study the authors analysed the results from 261 grafts that were evaluated by intra-operative transit time flow measurements (BF1001 (MediStim)) and underwent early post-operative coronary angiography (within 3 months from the surgery). Normal and failed graft indicators were compared according to the graft territories. Univariate logistic regression was used to obtain odds ratios for early grafts failure. Optimal mean flow (MF), pulsatility index and % backwards flow cut-off values to predict early graft failure were determined by means of ROC curve analysis and AUC. They found that for grafts to the left coronary system, a mean flow less than 15 ml/min, pulsatility index >5 and a backward flow of more than 4% predicted graft failure. For grafts to the right coronary artery, a mean flow of less than 20 ml/min, pulsatility index > 4.7 and backward flow more than 4.6% were predictive of failure. They concluded that transit time flow measurement may be a useful method of predicting early graft failure.

16. **Balacumaraswami et al. (2007).** In this review the two currently most commonly used modalities for intra-operative graft patency assessment; intra-operative fluorescence imaging and transit time flowmetry (MediStim) were compared and their value and limitations discussed. The analysis was based on a review of intra-operative fluorescence imaging studies performed between 2002 and 2005, transit time flowmetry measurements performed by the authors (BF2004 (MediStim)) and other transit time flowmetry studies performed between 1999 and 2005 (involving 100 patients or more). The authors commented that both systems can reliably detect occluded grafts but can not consistently detect minor abnormalities.

Transit time flowmetry provides a more objective measurement of graft flow compared to intra-operative fluorescence imaging but is more likely to under- or over-estimate the need for graft revision. Intra-operative fluorescence imaging may be more sensitive. In this study the authors state that MediStim and other manufacturers provided some financial support for equipment and disposables.

17. **Giammarco et al. (2006).** In this retrospective cohort study the possibility of predicting post-operative graft patency in coronary surgery by means of transit time flowmetry (CardioMed (MediStim)) was evaluated. The authors reported on 304 grafts in 157 patients submitted to intra-operative transit time flowmetry and post-operative angiography at a mean follow-up of 6.7± 4.8 months. Grafts were classified in two groups as completely functioning (group A) and failed (group B). Using an univariate analysis it was found that peak flow, mean graft flow (MGF), pulsatility index and % backwards flow were independent predictors for graft failure in 38 grafts. The authors concluded that the combination of the three major parameters (MGF, PI and %BF) results in a chance of predicting a graft failure within the first post-operative year.

18. **Gwozdziewicz et al. (2006).** The aim of this study was to determine the flow characteristics of individual and sequential bypass grafts created on the beating heart. A series of 50 patients undergoing off-pump coronary bypass surgery with at least one venous sequential coronary graft was used. Flow values and Pulsatility indexes were measured in both segments of the sequential graft using a CardioMed CM 4008 (MediStim) transit time flowmeter. Flow values were simultaneously compared to those of the individual venous graphs sutured to the same coronary arteries. It was concluded that the blood flow through an individual bypass was comparable with that through the distal segment of a sequential bypass. The grafting of a sequential bypass proximately to the larger artery in sequence did not appear to have a significant effect on the blood flow in the distal segment of a sequential bypass.

19. **Kim et al. (2005)** In this retrospective cohort study the authors assessed the validity of intra-operative transit time flowmetry (BF1001 (MediStim)) in predicting graft flow abnormalities. Transit time flow measurements and post-operative coronary angiography (as a patency control) was performed in 58 patients who underwent total arterial off-pump coronary artery bypass (OPCAB). A number of parameters including mean flow (MF) and pulsatility index (PI) were measured on and compared between 103 normal and 14 abnormal (occluded or competitive) grafts. Graft revision was planned for a mean flow <3 ml/min and pulsatility index >20. The validity of transit time flowmetry was assessed by comparing it with graft patency assessment from early post-operative angiography and the normal flow pattern of grafts anastomosed to the right and left coronary territories were reviewed. The results suggested that transit time flowmetry is a reliable tool for predicting graft flow impairment. Suggested criteria for predicting abnormal grafts were mean flow (MF) <15 ml/min and a pulsatility index (PI) >3 for the left coronary territories and >5 for the right coronary territories. The sensitivity and specificity of transit time flowmetry in detecting graft flow abnormality were 96.2% and 76.9%, respectively. The small sample size and the lack of a multivariate and ROC analysis were considered to be limitations of the study.

20. **Leong et al. (2005)** Graft patency in 116 patients who underwent coronary artery bypass grafting (CABG) was assessed using transit time flowmetry (Butterfly Flowmeter (MediStim)) in this retrospective cohort study. Six grafts with a high pulsatility index and low mean flow value were revised. The authors concluded that transit time flowmetry enables technical errors to be detected accurately in grafts. It was suggested that this technique should be mandatory in coronary artery bypass grafting.

21. **Kjaergard et al. (2004).** The purpose of this study was to measure blood flow in coronary artery bypass grafts both on-pump and off-pump and to estimate the total flow. The study included 120 patients having coronary artery bypass grafting on-pump and 97 patients having coronary artery bypass off-pump over a 3½ year period. Flow in the bypass vessels was measured using transit time flow methodology (CardioMed CM 1005

(MediStim)). The authors state that transit time flowmetry shows good correlation with directly measured blood flow and with Doppler ultrasound methods and it is more applicable for clinical measurements than the other methods. The study showed that there were no major differences in the vessel flow on-pump versus off-pump. Additionally, conventional coronary artery bypass grafting on-pump may restore up to about half of the normal resting coronary artery blood flow.

22. **Gwozdziewicz M. (2004).** The quality of constructed grafts was evaluated on 50 patients undergoing this procedure using the CardioMed CM 4008 (MediStim) transit time flow system. All of the sequential bypasses showed good per-operative quality. It was concluded that the use of a transit time flowmeter appears to be an effective tool for immediate patency verification in per-operative aortocoronary bypass techniques and should aid in preventing early graft occlusion.

23. **Walpoth et al. (1996).** Myocardial revascularization is performed preferentially with internal mammary artery grafts. Pedicle preparation and pharmacologic vasodilatory treatment vary greatly. The objectives of this study were the measurement of internal mammary artery graft flow with a transit-time flow technique (CardioMed (MediStim)), the comparison of two surgical take-down techniques for preparation of the pedicle (skeletonising vs standard preparation), the quantisation of transit-time flow compared to the free pedicle flow and the vasodilatory effect of papaverine on internal mammary artery flow. A wide range of transit-time flow measurements were made including at the beginning and end of take-down, after papaverine soaking and free flow into a beaker. The measurement of mean flow showed severe vasoconstriction of the internal mammary artery was detected regardless of the preparation technique. Papaverine soaking caused a moderate flow increase and a linear correlation was demonstrated between transit-time flow and free flow. The authors concluded that transit-time flow measurement is a reliable method for assessing internal mammary artery and coronary artery bypass flow.

Considering the simple technical application, the procedure may be regarded as a valuable instrument of quality control.

24. **Laustsen et al. (1996).** A study designed to validate the (*then*) new CardioMed CM 4000 (MediStim) transit time ultrasound apparatus for intra-operative measurement of volume blood flow in human patients. The study consisted of 25 patients undergoing vein grafting either in the leg or as a coronary bypass. During the operations volume blood flow was measured both by exsanguination from the cut vein and by use of the transit time flowmeter equipment. Within the examined blood flow range, the measurements determined by the transit time method agreed closely to the directly measured blood flow. The authors concluded that the transit time flowmeter apparatus was simple to use in an intra-operative setting and gave fast precise measurements of volume of blood flow.

25. **Walpoth et al. (1998)** Transit time flowmetry (CardioMed CM 4008 (MediStim)) was used to examine intra-operative graft flow and resistance in 46 patients with coronary artery disease. Invasive arterial pressure monitoring was done through a radial artery catheter. In 3 patients a low flow situation was found (flow <0.5 ml/min). By re-doing the graft anastomosis the flow was normalised to 15.7±9.6 ml/min ($p < 0.02$). The authors concluded that measurements of intra-operative flow and vascular resistance allow assessment of early graft function and prevent peri-operative infarction.

26. **Albäck et al. (2000).** Pre-operative angiographic characteristics of flow have emerged as a predicative factor for the upcoming of infrapopliteal reconstructions. Direct flow measurements can be routinely performed intra-operatively, but little was known (*at that time*) regarding the relationship of this parameter to graft outcome. This study compared the value of these parameters in predicting the mid-term patency of infrapopliteal bypass grafts using 172 cases. The pre-operative angiograms were scored using a standard methodology, at the end of each operation flow was measured with a transit time flowmeter (CardioMed CM 4006 (MediStim)). Follow-up consisted of pressure

measurements and duplex scanning. The authors concluded that graft flow and maximal flow capacity are good predictors of the one year graft patency of femorocrural bypasses.

27. **D'Ancona et al. (1999).** In this retrospective cohort study the ability of transit time flowmetry to improve the quality of information and increase the accuracy of diagnosing technical problems in bypass grafts was evaluated. At the time of the study transit time flow measurement was a (*comparatively*) new technology which the authors considered would improve the accuracy of graft flow measurement and yield real-time waveforms of graft flow. The use of the MediStim BF2004 transit-time flow meter was found to improve the surgical results by early detection of graft problems allowing immediate intra-operative revision. 161 patients underwent to off-pump coronary artery bypass grafting with a total of 323 grafts. All grafts were tested with transit time flowmetry. 32 grafts (9%) were surgically revised on the basis of an unsatisfactory flow curve or pulsatility index (>5) or both. The results showed that all the revised grafts were found to have a significant technical error, such as an intimal flap, thrombus, conduit kinking or dissection. No major complications, myocardial infarctions, or deaths in the entire series of patients were reported. The absence of control group with a gold standard of grafts verification and the clinical efficacy based only on the findings at graft revision were considered the limitations of this study.

22 of the studies (including both reviews (studies 4 and 16) but excluding the two studies previously reviewed (studies 2 and 8), the animal study (study 5) and the lower limb study (study 26)) use MediStim transit time flowmetry systems which predate the VeriQ but can be considered relevant to the decision problem. In all of these studies transit time flowmetry is used as a tool for assessing flow in coronary artery bypass grafts. The technique is generally considered as a valuable method or as a useful tool for predicting early graft failure with the ability to improve surgical results. Routine clinical use of transit time flowmetry is suggested (study 20). Several of the studies provide or propose criteria for predicting abnormal grafts in terms of limiting

values of parameters such as mean flow (MF) or mean graft flow (MGF), backwards flow (BF) and pulsatility index (PI).

4.4 *Additional studies identified by the EAC*

As mentioned in section 4.3 of this report, the manufacturer presented only four published studies and one guidelines document in the original submission. However, the EAC believed that because the manufacturer's search criteria were very strict, a number of relevant studies regarding the use of intra-operative transit time were not included in the clinical evidence. Following discussion with NICE and the EAC an additional list of studies was submitted by the manufacturer. 17 of these had previously been identified by the EAC as potentially relevant in their verification of the manufacturer's search strategy. Three further studies identified by the EAC (Appendix 3) and not included in the manufacturer's additional list of studies are summarised below.

Two of the studies (studies 1 and 2) compare transit time flowmetry and intra-operative fluorescence imaging (IFI). The third study (study 3) assesses the ability of transit time flowmetry to predict graft patency.

1. **Desai et al. (2006).** In this randomised controlled study intra-operative fluorescence imaging (IFI) was compared with transit time flowmetry (Butterfly Flowmeter (MediStim)) in 106 patients. 46 of these patients also underwent post-operative angiography control. Twelve of 139 (8.2%) grafts were demonstrated to have a 50% or greater stenosis. The sensitivity and specificity of intra-operative fluorescence imaging in detecting stenosis or occlusion was 83.3% and 100%, respectively. The sensitivity and specificity of transit time flowmetry was 25% and 98.4%, respectively. The difference in sensitivity between intra-operative fluorescence imaging and transit time flowmetry in detecting graft failure was significant (p=0023) and the authors concluded that intra-operative fluorescence imaging provides greater diagnostic accuracy for detecting graft errors.

2. **Balacumaraswami et al. (2005).** The authors compared the MediStim BF2004 transit time flowmetry system with intra-operative fluorescence

imaging (IFI) for assessing coronary artery bypass graft patency for 266 grafts. They found good correlation between measurements by the two techniques in 96% of grafts including 8 (3%) in patients who required revision. However, in a small proportion of patients (10%) it was suggested that graft patency assessment with transit time flowmetry alone might prompt unnecessary graft revision.

3. **D'Ancona et al. (2000).** The ability of transit time flowmetry in predicting graft patency was evaluated in this retrospective cohort study. 1145 grafts in 409 patients were analysed. 37 grafts were identified for revision due to abnormal transit time flowmetry findings. 34 were successfully revised, 3 showed no abnormal findings at revision. The authors concluded that evaluation with transit time flow measurements is valuable in determining the status of a graft after coronary artery bypass grafting.

As with the additional studies provided by the manufacturer (section 4.3 of this report), these studies identified by the EAC suggest that transit time flowmetry can be a useful tool for assessing flow in coronary artery bypass grafts and in predicting early graft failure. However, one study (study 1) suggests that intra-operative fluorescence imaging provides greater diagnostic accuracy than transit time flowmetry for detecting graft errors and one study (study 2) points out that in a small proportion of patients graft patency assessment with transit time flowmetry alone might prompt unnecessary graft revision.

5 Assessment of cost analysis

5.1 *Overview of manufacturer's economic assessment*

5.1.1 Methods

This section assesses the cost analysis submitted by the manufacturer regarding the use of VeriQ system for the intra-operative assessment of graft patency in patients undergoing CABG surgery. The manufacturer's submission includes:

- A description of the literature search undertaken by the manufacture for the identification of cost and cost effectiveness studies in relation to the VeriQ system
- Extracts from the *de novo* cost analysis that was conducted, including, data sources and sensitivity analyses
- An Excel file showing the base case results and sensitivity analyses (Executable Excel speared sheet).

A summary of the relevant areas of the manufacturer's submission document for the cost analysis is shown in Table 4.

Table 4: Summary of key information for cost analysis

	Reference in submission document	**Key tables/figures in submission document**
Review of literature	p48 to 52	-
Model structure	p52	-
Transition probabilities	P55 to 64	-
Time horizon	p53	Table B9
Adverse events	p71	-
Resource use and costs	p8, p57 to 86	Table A1, Table B10, B14, B16
Sensitivity analysis	p76 to 86	-
Results	p72 to 86	-

EAC note: Due to a typographic error in entering the labour costs for nurses into the Excel file, many of the figures throughout the manufacturer's submission are incorrect. It was also noted that the incorrect figures were

used for the PS probe costs in the Excel spreadsheet. The PS probe costs set out in table A1 of the manufacturer's submission were not used to arrive at the average cost per treatment presented at the bottom of that table. The cost per patient scanned are based on the purchase cost of the VeriQ system divided by 220 day a year use over 10 years plus the cost of the PS probe divided by 30 uses multiplied by the 1.7 probes used (average) per patient scanned.

Table 5. Tables with incorrect data in the manufacturer's submission

Table number or description in manufacturer's submission	Page number in manufacturer's submission
A1	8
B10	57 to 63
Bottom of page 70	70
B16	76 to 78
B17	79
Variable values	79, 80
Sensitivity analysis	81
Sensitivity analysis	84, 85

The EAC reworked the cost model with the PS probe costs, as stated in table A1 of the manufacturer's submission and the correct figures for the nurses pay. The results are shown in table 6 of this report, the associated sensitivity analysis is shown in table 7 of this report.

Identification of studies

The search strategy for cost-effectiveness studies is reported in Appendix 6 of the manufacturer's submission, Search strategy for cost-effectiveness and cost studies (section 6.1, pages 104 to 106). The manufacturer's submission includes a search of the Medline, Embase, Medline (R), EconLIT and NHS EED databases.

The search strategy presented in the manufacturer's submission is considered appropriate to identify relevant literature but was inadequately reported. There was a lack of detail in the description of the manufacturer's searches for the studies. The manufacturer's submission states that the same search strategy

(as described in Appendix 6, page 105 of the manufacturer's submission) was applied in all searched databases.

The terms used in the search strategy presented in the manufacturer's submission are considered to be rather generic and not extensive. The use of such a search has the risk of missing relevant studies. Terms such as 'cost-effectiveness' and 'cost-benefit' could also have be used as additional search terms. The EAC also noted the absence of the use of any subject index headings (for example MeSH) but the use of these did not change the resultant literature found.

Two studies were identified by the manufacturer's literature search. The EAC agreed with the manufacturer, that the two identified studies are not relevant and that there appears to be no relevant literature available on the cost effectiveness of transit time flowmetry. There is no indication that any limits were applied to the search strategy. The EAC literature search did not find any relevant literature on the cost effectiveness of the VeriQ or transit time flowmetry, even when using different search strategies.

Data from two studies identified in the clinical effectiveness searches were used extensively within the cost model (Kieser et al. (2010) and Becit et al. (2007)). The EAC considers the use of this data to be appropriate. A third paper (Kim et al. (2010)) was identified but excluded on the grounds that it was reporting on older technology, the EAC agrees with this exclusion.

There is no indication that any limits were applied to the search strategy.

Model structure

A de novo cost analysis was constructed for the manufacturer to assess the cost savings to the NHS of introducing the VeriQ 2011 transit time flowmetry technology for the intra-operative assessment of the patency of grafts during all CABG surgery. The model was presented as part of the manufacturer's submission as an executable Excel file, extracts from this model were presented in the submission. The cost model was considered appropriately structured allowing for the manufacturer's criteria for the assessment of the

VeriQ by the EAC. Patient types used in the model were all those under going CABG surgery per year.

Due to the lack of cost analysis studies (none were identified during the literature search (Section 7 of the manufacturer's submission)), it was not possible for the manufacturer to have a formal model structure constructed. The savings generated by the reduced incidence of MACE, etc, were calculated per patient scanned on a bottom-up approach. The additional length of the operation time required due to the use of the VeriQ was taken in to account in the cost model calculations by working out the cost of the CABG team per minute. It is clear from the model that an assumption that one VeriQ system will be used by one CABG team, no allowance was made for the VeriQ to be shared or used to assess grafts other than CABG. No allowance was made for the use of the other function of the VeriQ, only the transit time flowmetry (TTFM) function was considered in the cost model. This is consistent with the scoop set out by NICE. Only the additional costs of using of the VeriQ were considered, not the total cost of CABG surgery, as all other costs remain the same and only the additional incremental costs of the use of the VeriQ against the benefits of the use of the VeriQ need to be addressed. The EAC agrees with this approach. Training costs were not included in the model (the manufacturer has stated that this will be provided free of charge), however the time required for the training was also left out of the model. The optional service maintenance costs were also omitted from the cost model.

Health States

The manufacturer has not identified any health states; the EAC considers this appropriate as the VeriQ is a diagnostic tool so there are no relevant health state changes to consider.

Assumptions

A list of the labour costs used in the *de novo* economic model are provided in the manufacturer's submission (Table B10, page 57 to 63 and Table B11, page 70 (**EAC note:** Table B11 is correct)). The justifications for these assumptions are set out on pages 65 to 67 (of the manufacturer's

submission). These assumptions are applied throughout the economic model and the EAC confident that these assumptions are valid. It is clear that the assumption that one VeriQ system will be used by one CABG team was used in calculating the cost of probes used per patient.

Data sources

The main data sources for the model include; NHS pay scales, PbR tables 2009-2010, UK government statistic, data from various websites (identified in the submission), Kieser et al. (2010), Becit et al. (2007) and personal communications with Dr Kieser (e-mail) and Dr Bergsland (oral).

All data sources used by the manufacturer were reviewed by the EAC and were found acceptable.

Resources and costs

The costs included in the model are based on using the VeriQ 2011 with a PS probe to assess patency of grafts during CABG surgery. The costs are compared against clinical evaluation (the selected comparator); the cost of complications resulting from CABG surgery are also considered.

Table 5: Cost and resource implications to the NHS

Parameter	Range	Base case*
Duration of TTFM per procedure, mins	2 to 5	2.35
No of probes per procedure	1.4 to 2	1.7
Cost of probe per use, £	61.29 to 62.30	61.29**
Probe uses	30 to 50	30
Rate of Patient with revisions, %	2.20 to 14.6	6.58
Duration minor revision, mins	2 to 5	2.5
Duration major revision, mins	27 to 57	42
Rate of minor revision, %	20 to 50	34.7
Cost of re-operative procedure, £	80 to 288	180.41
Re-operative procedure rate, %	0.6 to 8.5	3.0
Cost of deep sternal infection, £	687 to 1425	860.55
Deep sternal infection rate, %	0.0 to 5.5	1.0
IABP cost, £	1968 to 3346	2657.37
IABP rates, %	**0.0 to 13.9**	**1.0**
MI costs, £	1267 to 2067	1666.96
MI rates, %	**0.0 to 11.3**	**0.0**
Cost of CABG team per min, £	2.63 to 4.96	4.16

Notes: * Figure supported by the literature or advise. **This appears to be the for PS probe.

The range across which the parameters were considered (table 5 above) was taken from various sources; the EAC considers the range and base case values to be appropriate. The cost and number of uses of a VeriQ probe and the number of probes used per procedure were supplied by the manufacturer. The manufacturer states that the costs of a re-operative procedure, deep sternal infection, IABP and MI are taken from NHS reference costs 2009 - 2010. The rate of complication is taken from the literature (Kieser et al. (2010) and Becit et al. (2007)). The cost of the CABG team is derived from a number of sources including 'NHS careers' and 'Government statistics'. The composition of a typical CABG team of six is taken from data available from the University of Maryland Medical Center and was considered appropriate by the NICE appointed experts. The time taken for minor and major revisions of grafts was supplied in communications with Dr Kieser and Dr Bergsland. However, the NICE appointed experts considered that the maximum time for a major revision should be 30 minutes; this shorter time would make use of the VeriQ more cost effective. The rates of minor and major revisions are taken form the literature (Kieser et al. (2010) and Becit et al. (2007)). The manufacturer's justification for these assumptions is set out on pages 65 to 68 of the manufacturer's submission, the rational for these assumptions is considered to be sound to the EAC.

Transition probabilities

No formal model structure has been considered in the manufacturer's submission, there are no health states to transition between and therefore transition probabilities are not required, the EAC is in agreement with this.

Time horizon

The time frame covers a period from more than one year (Becit et al. (2007)) to up to three years after CABG (Kieser et al. (2010)). There was no extrapolation beyond this point.

Discounting

No discounting is considered in the manufacturer's submission.

Sensitivity analysis

A deterministic sensitivity analysis was undertaken. A probabilistic sensitivity analysis was not possible as no appropriate formal model was identified. The EAC is in agreement with this.

The follow parameters were individually investigated using the sensitivity analysis:

- Duration of TTFM per procedure, minutes
- No of probes per procedure
- Rate of Patient with revisions, %
- Duration minor revision, minutes
- Duration major revision, minutes
- Rate of minor revision, %
- Cost of re-operative procedure, £
- Re-operative procedure rate, %
- Cost of deep sternal infection, £
- Deep sternal infection rate, %
- IABP cost, £
- IABP rates, %
- MI costs, £
- MI rates, %
- Cost of CABG team per minute, £

5.1.2 Results

The results are presented in terms of the costs saving per patient scanned with the VeriQ 2011 using the PS probe. The incremental costs of the scans per patient have been off-set against the costs incurred due to the predicted higher incident of MACE in those patients whose grafts are not scanned (this is supported by the literature). The total cost of the CABG operation has not been worked out as the only change are the cost of undertaking the transit

time flowmetry scan, the cost for this has been broken down into staff time and the cost of the use of the technology. The cost and time needed to train staff in the use of the VeriQ has not been included in the cost model. The manufacturer states that they will cover the cost of training. The theory training should last half a day, the practical training can take place during CABG surgery with minimal delay to the operation (quote from manufacturer).

Table 6 (below) shows the reworked manufacturer's 'Base Case' using the correct pay figures for the nurses and the correct price of the PS probe taken the manufacturer's submission (table A1, page 8). Table 7 (below) shows the sensitivity analysis associated with this base case.

Table 6. Manufacturer's Base Case reworked with correct nurses' pay and correct PS probe price of £1,582

Resource factor	CABG w/TTFM			CABG			Difference		
	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			9.79			0.00			9.79
Probes used	1.7	probes		0	probes		1.7	probes	
Probe cost			104.19			0.00			104.19
Cost of TTFM use per patient			**113.98**			**0.00**			**113.98**
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			10.41			0.00			10.41
Team cost of minor revision per patient			**0.24**			**0.00**			**0.24**
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			174.93			0.00			174.93
Team cost of major revision per patient			**7.52**			**0.00**			**7.52**
Sum of TTFM costs			**121.73**			**0.00**			**121.73**

Consequences of not doing TTFM					
Intra-operative 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 infection, rate	1.00%		1.00%	0.00%	
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**
Post-operative issues:					
Peri-operative MI, rate	0.00%		5.00%	-5.00%	
Peri-operative 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		**162.32**		**283.38**	**-121.06**

Table 7. Manufacture sensitivity analysis with correct nurses' pay and PS probe cost.

		Variable values						Width of interval
Variable	Best Case		Base Case	Worst Case		Delta Cost values, £		£
Duration of TTFM per procedure, min		2	2.35	5		-122.51	-121.06	-110.02	12.49
Mean No. of probes per procedure		1.4	1.7	2		-139.44	-121.06	-102.67	36.77
Rate of pats with revisions		2.20%	6.58%	14.60%		-126.22	-121.06	-111.61	14.61
Duration of minor revisions, min		2	2.5	5		-121.10	-121.06	-120.82	0.29
Duration of major revisions, min		27	42	57		-123.74	-121.06	-118.37	5.37
Relative rate of minor revisions		50.0 %	34.7 %	20.0 %		-122.71	-121.06	-119.46	3.25
Re-operative procedures, cost (£)		288.00	180.41	80.00		-121.06	-121.06	-121.06	0.00
Re-operative procedures, rates	0.6 %	8.5 %	3.0 %	8.5 %	0.6 %	-135.31	-121.06	-106.80	28.50
Deep sternal infection, cost (£)		1425.00	860.55	687.00		-121.06	-121.06	-121.06	0.00
Deep sternal infection, rates	0.0 %	5.5 %	1.0 %	5.5 %	0.0 %	-167.70	-121.06	-74.42	93.28
IABP, cost (£)		3346.00	2657.37	1968.00		-162.38	-121.06	-79.70	82.68
IABP, rates	0.0 %	13.9 %	1.0 %	3.5 %	3.5 %	-329.93	-121.06	38.38	368.31
MI, costs (£)		2067.00	1666.96	1267.00		-141.06	-121.06	-101.06	40.00
MI, rates	0.0 %	11.3 %	0.0 %	2.5 %	2.5 %	-225.74	-121.06	-44.00	181.74
Cost of CABG team composition, (£)		2.63	4.16	4.96		-127.51	-121.06	-117.72	9.79
On-pump rate		70.0 %	80.0 %	90.0 %		-121.12	-121.06	-121.00	0.12

5.1.3 Model validation

A de novo cost analysis was conducted for the manufacturer to assess the cost savings to the NHS of the introduction of the VeriQ system for the intra-operative assessment of graft patency in CABG patients. The model was presented in the manufacturer's submission as a separate executable Excel file, which is considered acceptable by the EAC. The number of patients used in the model were all (28,000) patients who underwent CABG.

5.2 *Critique of approach used*

The manufacturer has spread the cost of purchasing the VeriQ 2011 equipment over 10 years and the purchase of the PS probes over 30 uses. The optional service/maintenance costs have not been included.

In the submission the manufacturer states that the cost of the training will be provided free of charge but the time for the training (half of one day of theory) has not be considered.

A comparative cost analysis of using the VeriQ system in CABG against clinical assessment was the scope of the analysis issued by NICE. The manufacturer's submission conducted an analysis of cost savings to the NHS where the VeriQ was used to assess patency of grafts intra-operatively allowing immediate revision of defective grafts. The savings of not requiring a post-operative angiogram were not considered.

All figures and assumptions used by the manufacturer are supported either by the literature or in consultation with experts (Dr Kieser and Dr Bergsland) and are considered appropriate by the EAC.

In summary, the EAC found that although there was a typographical error made in entering the wages of the nurses, the incorrect value for the cost of the PS probe was used and time for training was excluded, the model as a whole was considered accurate and simple to use giving reliable and consistent results which reflected real world cases.

5.3 *Results included in manufacturer's submission*

The results of the cost model are presented in the cost analysis spreadsheet; the results of the base case analysis are reported in the manufacturer's submission (table B16, pages 76 to 78) and the results of sensitivity analysis are also reported in the submission document (tables on pages 81 to 85). It should be noted that the labour costs used in the cost analysis spreadsheet for the nurses suffered from a typographical error which made the figure in the submission slightly less favourable to the VeriQ. Also the wrong price for the cost of the PS probe (cardiac size 1.5 to 7mm) was used in the manufacturer's model.

The labour costs presented in table B11 (page 70) of the manufacturer's submission are correct, however all other figures in the submission which relate to labour cost are incorrect due to the typographical error in the executable Excel file. Tables with the correct figures are presented in Appendix 5 of this report.

The cost saving in the base case reported in the manufacturer's submission per patient scanned to the NHS using the VeriQ 2011 is £125.15p (table B16, pages 76 to 78). This figure is incorrect, the correct figure is £121.06p. This is based on the use of the VeriQ 2011 (over 10 years) with the PS probe (30 uses).

Table 8. Summary of the base case analysis costs *(corrected by EAC)*

	Using VeriQ TTFM	**Clinical assessment**
Graft assessment	£121.73	0.0
Operative issues	£40.59	£283.38
Total cost per patient	£162.32	£283.38
Saving from VeriQ	£121.06	

Note: Full table presented in table 6 of this report.

Around 28,000 CABG operations are performed each year in the UK (http://www.patient.co.uk/doctor/Coronary-Artery-Bypass-Grafting.htm) and with a saving of £121.06p per patient, the NHS could potentially save £3,389,680 if all of the CABG patients were scanned using the VeriQ peri-operatively. The EAC is not aware as to how many VeriQ systems would need to be purchased for the NHS and this is not covered in the manufacturer's

submission. As the savings are based on each patient scanned, the savings to the NHS per patient are not dependent on the number of VeriQ systems in use. However, the savings to the NHS as a whole will depend on the number of VeriQ systems in use.

After consultation with the NICE appointed experts, the EAC believes that it must be taken in to consideration that if the surgeons are fully confident the graft is sound they will not use transit time flowmetry but would use the VeriQ when the clinical assessment is ambiguous; this would result in a completely different, 'cost effective' model being required.

From the sensitivity analysis results in table 7 of this report, it can be seen that the range of savings from the manufacturer's best case scenario to the worst case scenario is between a saving of £329.93p and a cost of £38.38p per patient scanned. The only scenario presented by the manufacturer in the submission which results in a net cost to the NHS is the worst case scenario where the rate of IABP is the same for both arms of the sensitivity analysis with the lowest repayment costs from the work undertaken. The EAC feel this is an unnecessary bleak view and that the VeriQ is likely to save the NHS money if utilised appropriately. The expenditure to the NHS as a whole if all 28,000 CABG patients were scanned would be between a saving of £9,238,040 and a cost of £1,074,640 these figures represent the very best case and the very worst case scenarios form the manufacturer's submission.

It can also be seen in table 7 of this report that the variables with the greatest impact on cost effectiveness in the model are IABP and MI rates with width intervals of £368.31p and £181.74p respectively.

For the base case scenario it is assumed that the cost of purchasing the VeriQ 2011 is spread over the predicted 10 years anticipated lifespan of the system and that the cost of the PS probe spread over 30 uses. However, the price of £1,500 of the PS probe was taken from an early document and not the later manufacturer's submission (which states the probe price of £1,582). The base case was reworked by the EAC to allow for updated probe price of

£1,582. The summary results are shown in table 9 (full results in table 8 of this report).

It can be seen that the VeriQ system still saves the NHS money per patent scanned in the base case. Even allowing for the current probe cost the net saving to the NHS as a whole from the base case would be £280,616 if all CABG patients were scanned.

VeriQ PQ probe

The EAC reworked the cost model to reflect the use of the PQ probe with the VeriQ 2011. The PQ probe (cardiac size 1.5 to 5 mm) for VeriQ system has a longer predicted life expectancy of 50 uses at the same price of £1,582, as the PS probe (cardiac size 1.5 to 7 mm); this would change the cost effective analysis as shown below. As can be seen this change reduces the cost of using the VeriQ system.

Table 9. Summary of base case using the PQ probe and current price

	Using VeriQ TTFM	Clinical assessment
Graft assessment	£85.37	£0.00
Operative issues	£40.59	£283.38
Total cost per patient	126.46	283.38
Saving from VeriQ	156.92	

Note: Full table shown in appendix 5, table 1, of this report

This would result in a saving to the NHS as a whole of £4,393,760 per year with the best case saving (table 2, appendix 5 of this report) of £10,239,600 and the worst case costing £70,560.

Servicing and 250 days use

The EAC also reworked the cost model to taken into account the costs of the optional service/maintenance contract of £1,800 per year after the first two years. The first two years of service/maintenance are included in the purchase price. In this scenario the EAC also increased the days use per year to 250 days allowing for more than one CABG team to make use of a single VeriQ system.

Table 10. Summary of base case including servicing and 250 days a year use.

	Using VeriQ TTFM	Clinical assessment
Graft assessment	£125.75	£0.00
Operative issues	£40.59	£283.38
Total cost per patient	£166.34	£283.38
Saving from VeriQ	£117.04	

Note: Full table shown in appendix 5 table 3, of this report

This would result in a saving to the NHS as a whole of £3,277,120 per year with the best case saving (table 4, appendix 5 of this report) of £9,125,480 and the worst case costing £1,187,200.

No assessment was made by the manufacturer or the EAC of the cost effectiveness of the higher specification versions of the VeriQ (2111 and 4122). The purchase of these systems would depend on local requirements and demands.

5.4 *Comment on validity of results presented with reference to methodology used*

The results shown in the manufacturer's submission are incorrect; the correct figures are shown in table 6 and 7 of this report. The figures indicate that the VeriQ 2011 is likely to provide a cost saving across the NHS. In the sensitivity analysis the VeriQ 2011 saved the NHS money except when the rate of patients being put on IABP was the same for both those patients who are scanned with the VeriQ as those not scanned. A small change in the IABP rate in the worst case scenario (of less than two percent) can result in the VeriQ always showing a saving to the NHS. All other variables used resulted in a saving to the NHS in all of the worst cases. The assumptions made in the cost model appear to be coincident with real life cases.

5.5 *Summary of uncertainties and issues*

The EAC considered the manufacturer's submission in relation to the cost impact of the VeriQ 2011 to be just adequate in addressing the decision problem. A sensitivity analysis was conducted in order to explore the robustness of the results to change of various parameters. The main issues raised by the EAC are summarised below.

Literature searches

The search strategies provided in the Analysis of Cost section of the submission are not adequately reported; therefore the EAC is not confident about the identification of studies and whether all relevant studies were included in the submission. However the EAC did not find any other relevant studies when undertaken its own literature search.

Data sources

The main data sources for the model are NHS pay scales, PbR tables 2009-2010, UK government statistics, various websites (identified in the submission), two published papers i.e. Kieser *et al* (2010), Becit *et al* (2007) and private communication with Dr Kieser (e-mail) and Dr Bergsland (oral).

Execution of the model

Details of the model are inadequately reported in the submission. However, the model is simple to execute and appears to give reliable results which are repeatable.

Adverse events

No adverse events resulting from the use of the MediStim VeriQ were reported and hence no adverse event costs need to be taken into account.

Additional work undertaken by the External Assessment Centre (EAC)

Additional work undertaken by the EAC comprised:

- Additional literature searches in order to investigate the reliability of the manufacturer's literature searches that were used to identify the clinical effectiveness of the intervention
- Review of additional list of studies (27) submitted by the manufacturer
- Review of additional studies (3) identified as relevant by the EAC
- Comments have been provided alongside the manufacturer's critical appraisal of the included clinical effectiveness studies
- Re-running all of the executable Excel file using corrected/new data
- Additional base cases were run (Appendix 5 of this report)
- Additional sensitivity analyses have been undertaken (Appendix 5 of this report)

Search in Pubmed replicating manufacturer's search strategy (03/03/11) for literature on clinical effectiveness

Search	Most Recent Queries	Time	Result
#13	Search (#7) AND #11 Limits: Publication Date from 2004 to 2011	05:18:52	138
#12	Search (#7) AND #11	05:18:26	281
#11	Search ((#8) OR #9) OR #10	05:18:03	46835
#10	Search CABG	05:17:44	10291
#9	Search 'coronary artery bypass'	05:17:29	45904
#8	Search 'coronary artery graft'	05:16:36	96
#7	Search (((((#1) OR #2) OR #3) OR #4) OR #5) OR #6	05:16:19	97837
#6	Search pi or mf	05:15:34	85282
#5	Search 'mean flow'	05:15:18	1887
#4	Search 'pulsatility index'	05:15:05	3039
#3	Search ttf or ttm	05:14:51	2291
#2	Search transit-time	05:14:30	7286

#1	Search 'transit time flow'	05:14:12	221

EAC Pubmed search

((‘transit time flow’[All Fields] OR transit-time[All Fields] OR (ttf[All Fields] OR ttm[All Fields]) OR ‘pulsatility index’[All Fields] OR ‘mean flow’[All Fields] OR (pi[All Fields] OR mf[All Fields])) AND (CABG[All Fields] OR ‘coronary artery bypass’[All Fields] OR ‘coronary artery graft’[All Fields])) AND (‘2004’[PDAT]: ‘2011’[PDAT])

Cost Effectiveness search

Search in Pubmed replicating manufacturer’s search strategy for cost effectivness. (01/04/11)

Search	Most Recent Queries	Time	Result
#13	Search ((#10) AND #11) AND #12)	11:46:43	2
#12	Search (#8) OR #9	11:46:00	684772
#11	Search (((#4) OR #5) OR #6) OR #7)	11:45:38	12313
#10	Search #1) OR #2) or #3)	11:43:56	54320
#9	Search cost	11:42:56	479595
#8	Search economic	11:42:40	584009
#7	Search ttfm	11:42:16	25
#6	Search ttf	11:42:04	1754
#5	Search transit-time	11:41:47	7315
#4	Search transit time	11:41:36	10565
#3	Search cabg	11:41:20	10342
#2	Search coronary artery graft	11:39:32	16834
#1	Search coronary artery bypass	11:37:19	50570

((coronary artery bypass[All Fields] OR coronary artery graft [All Fields] OR cabg [All Fields]) AND (transit time [All Fields] OR transit-time [All Fields] OR ttf [All Fields] OR ttfm [All Fields]) AND (economic [All Fields] OR cost [All Fields])

The two studies found were the same as those identified by the manufacturer; neither study is considered relevant by the EAC to the cost of the use of the VeriQ system.

6 Discussion

6.1 *Summary of clinical effectiveness issues*

Early graft patency can influence the outcome, either early or late, of coronary artery bypass grafting and therefore the assessment of the quality of the anastomosis is of great importance. A number of methods are available including post-operative angiography, intra-operative fluorescence imaging and transit time flowmetry.

This report assesses the submission to NICE (by the manufacturer (MediStim ASA) of the use of the VeriQ transit time flowmetry system during surgery for assessing graft flow in patients undergoing coronary artery bypass surgery. The number of supporting documents submitted with the original manufacturer's submission was small (four studies and one guidelines document). Therefore, at the request of NICE and the EAC, 27 additional studies were submitted at a later date. Most of these studies used MediStim transit time flowmetry systems which predate the VeriQ but operate on similar principles. Three further studies, not included in the manufacturer's additional list, were identified by the EAC as relevant. All of the studies were reviewed by the EAC.

In the majority of studies (both the original and additional studies) transit time flowmetry was used as a tool for assessing flow in coronary artery bypass grafts. In general, the technique is considered a useful method of predicting early graft failure and routine clinical use is suggested by a number of authors. Criteria for predicting abnormal grafts are presented or proposed in terms of limiting values for a range of measured parameters. However, in one study it is pointed out that the measured values can depend on the type and manufacturer of the system and on the system settings. Therefore it is important that both the type of flowmeter and system settings are clearly indicated to ensure consistency in graft flow measurements.

6.2 *Summary of cost issues*

The cost literature search is inadequately reported and the two studies identified have no bearing on the cost effectiveness of the VeriQ 2011 for transit time flowmetry (TTFM) of CABG.

The cost data used by the manufacturer is supported by evidence; however some of this is in private communications. The (corrected) base case demonstrated that the saving to the NHS per patents scanned is £121.06p with a possible saving to the NHS as a whole of £3,389,680 if all 28,000 patients per year who undergo CABG are scanned using the VeriQ 2011 with the PS probe (30 uses).

If the PQ probe (50 uses) is used the base case shows a saving of £156.92p per patient scanned with a possible saving of up to £4,393,760 per year to the NHS. If a mixture of both probes were required due to vessel size the saving would fall between these figures.

When service costs and 250 working days a year are considered, the base case saving is £117.04p per patient scanned with a possible saving to the NHS of £3,277,120 per year.

The other scenarios run by the EAC also show a saving to the NHS in the base case. All scenarios run show the same sensitivity to changes in the IABP rate and a small change in the IABP rate in the worst case scenario (of less than two percent) can result in the VeriQ always showing a saving to the NHS.

The cost effectiveness of the higher specification versions of the VeriQ (2111 and 4122) was not assessed by the manufacturer or the EAC.

6.3 *Implications for guidance and research*

If the use of the transit time flowmetry become a regular test in CABG procedures, data could be collected to verify the cost effectiveness of the technique in routine use.

The use of the VeriQ transit time flowmeter system for the assessment of the patency of grafts during liver and renal transplant and revascularisation due to

critical limb ischaemia could be investigated. A single VeriQ system could be used for a range of investigations (with the appropriate probes).

The main comparator considered in this report is Clinical Assessment. It may be useful to consider transit time flowmetry and the VeriQ against other comparators in order to further investigate clinical and cost effectiveness.

Appendix 1: Included and excluded studies considered for review from manufacturer's submission

Studies 2, 3, 12, 14 (clinical effectiveness studies) and 15 (guidelines document) were identified as being relevant by the manufacturer and included in the manufacturer's submission, the remaining studies were excluded.

1. Mack MJ. **Intra-operative coronary graft assessment.** *Current Opinion in Cardiology*. 23(6), 568-72, Nov 2008.

2. Kieser TM, Rose S, Kowalewski R and Belenkie I. **Transit-time flow predicts outcomes in coronary artery bypass graft patients: a series of 1000 consecutive arterial grafts.** *European Journal of Cardiothoracic Surgery*. 38, 155-162, 2010.

3. Becit N, Erkut B, Ceviz M, Unlu Y, Colak A and Kocak H. **The impact of intra-operative transit time flow measurements on the results of on-pump coronary surgery.** *European Journal of Cardiothoracic Surgery*. 32, 313-318, 2007.

4. Jalal A. **Work in Progress Report - An objective method for grading of distal disease in the grafted coronary arteries.** *Interactive CardioVascular and Thoracic Surgery*. 6, 451-455, 2007.

5. Nordgaard H, Nordhaug D, Kirkeby-Garstad I, Løvstakken L, Vitale N and Haaverstad R. **Different graft flow patterns due to competitive flow or stenosis in the coronary anastomosis assessed by transit-time flowmetry in a porcine model.** *European Journal of Cardiothoracic Surgery*. 36, 137-142, 2009.

6. Trachiotis GD. **Letter to the Editor - Value of diastolic flow with transit-time flow meters in coronary artery bypass surgery.** *European Journal of Cardiothoracic Surgery*. 39**,** 431, 2011.

7. Nordgaard H, Vitale N and Haaverstad R. **Reply to letter to the Editor (Study 6 above).** *European Journal of Cardiothoracic Surgery*. 39, 431, 2011.

8. Colli A and Ruyra X. **Routine intra-operative completion angiography after coronary artery bypass grafting or routine intra-operative transit time flow measurement to check graft's quality?** *Journal of the American College of Cardiology*. 54, 2337-2338, 2009.

9. Leacche M, Balaguer JM and Byrne JG. **Intra-operative Grafts Assessment.** *Seminars in Thoracic and Cardiovascular Surgery*. 21, 207-212, 2009.

10. Singh SK, Desai ND, Chikazawa G, Tsuneyoshi H, Vincent J, Zagorski BM, Pen V, Moussa F, Cohen GN, Christakis GT and Fremes SE. **The graft imaging to improve patency (GRIIP) clinical trial results.** *Journal of Thoracic and Cardiovascular Surgery*. 139, 294-301, Feb 2010.

11. Kim K-B, Kim JS, Kang H-J, Koo B-K, Kim H-S, Oh B-H and Park Y-B. **Ten-year experience with off-pump coronary artery bypass grafting: Lessons learned from early post-operative angiography.** *Journal of Thoracic and Cardiovascular Surgery*. 139, 256-262, 2010.

12. Nordgaard H, Vitale N, Astudillo R, Renzulli A, Romundstad P and Haaverstad R. **Pulsatility index variations using two different transit-time flowmeters in coronary artery bypass surgery.** *European Journal of Cardiothoracic Surgery*. 37(5), 1063-67, 2010.

13. Hatada A, Okamura Y, Kaneko M, Hisaoka T, Yamamoto S, Hiramatsu T and Nishimura Y. **Comparison of the waveforms of transit-time flowmetry and intra-operative fluorescence imaging for assessing coronary artery bypass graft patency.** *General Thoracic and Cardiovascular Surgery*. 59(1), 14-18, 2011, Epub 12 Jan 2011.

14. Jokinen JJ, Werkkala K, Vainikka T, Peräkylä T, Simpanen J and Ihlberg L. **Clinical value of intra-operative transit-time flow measurement for coronary artery bypass grafting: a prospective angiography controlled study.** *European Journal of Cardiothoracic Surgery*. In press, corrected proof available online, 20 November 2010.

15. The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). **Guidelines on myocardial revascularisation.** *European Heart Journal*. 31, 2501-2555, 2010 (paragraph 10.2.2).

Appendix 2: Additional studies submitted by the manufacturer

1. Beran E, Kapitan M, Mächler H, Salaymeh L, Anelli-Monti M, Oberwalder P, Berghold A and Tscheliessnigg K. **Accurate pre-operative echocardiography has more impact on prediction of long-term mortality than intra-operatively measured flow in coronary bypass grafts.** *European Journal of Cardiothoracic Surgery*. In press, corrected proof available on-line, 14 December 2010.

2. Jokinen JJ, Kalervo Werkkala K, Vainikka T, Peräkylä T, Simpanen J, and Ihlberg L. **Clinical value of intra-operative transit-time flow measurement for coronary artery bypass grafting: a prospective angiography-controlled study.** *European Journal of Cardiothoracic Surgery*, In press, corrected proof available online, 20 November 2010.

3. Mack MJ. **Intra-operative coronary graft assessment.** *Current Opinion in Cardiology*. 23(6), 568-72, Nov 2008.

4. Jalal A. **Work in Progress Report - An objective method for grading of distal disease in the grafted coronary arteries.** *Interactive CardioVascular and Thoracic Surgery*. Work in progress report. 6, 451-455, 2007.

5. Nordgaard H, Nordhaug D, Kirkeby-Garstad I, Løvstakken L, Vitale N and Haaverstad R. **Different graft flow patterns due to competitive flow or stenosis in the coronary anastomosis assessed by transit-time flowmetry in a porcine model.** *European Journal of Cardiothoracic Surgery*. 36, 137-142, 2009.

6 Hatada A, Okamura Y, Kaneko M, Hisaoka T, Yamamoto S, Hiramatsu T and Nishimura Y. **Comparison of the waveforms of transit-time flowmetry and intra-operative fluorescence imaging for assessing coronary artery bypass graft patency.** *General Thoracic and Cardiovascular Surgery*. 59(1), 14-18, 2011, E-publication 12 January 2011.

7 Economopoulos V, Psaltis E, Kelpis T, Pitsis A. **Subclavian artery stenosis detected with transit-time flowmeter during OPCAB.** *Journal of Cardiac Surgery*. 25, 176, 2010.

8. Nordgaard HB, Vitale N, Astudillo R, Renzulli A, Romundstad P and Haaverstad R. **Pulsatility index variations using two different transit-time flowmeters in coronary artery bypass surgery.** *European Journal of Cardiothoracic Surgery*. 37(5), 1063-1067, May 2010, E-publication 23 December 2009.

9. Takami Y, Tajima K, Terazawa S, Okada N, Fujii K and Sakai Y. **Transit-time flow characteristics of in situ right gastroepiploic arterial grafts in coronary artery bypass grafting.** *Journal of Thoracic and Cardiovascular Surgery*. 138, 669-673, 2009.

10. Nordgaard H, Vitale N and Haaverstad R. **Transit-time blood flow measurements in sequential saphenous coronary Artery bypass grafts.** *Annals of Thoracic Surgery*. 87, 1409-1415, 2009.

11. Weber A, Tavakoli R and Genoni M. **Superior flow pattern of internal thoracic artery over saphenous vein grafts during OPCAB procedures.** *Journal of Cardiac Surgery*. 24, 2-5, 2009.

12. Tokuda Y, Song MH, Oshima H, Usui A and Ueda Y. **Predicting midterm coronary artery bypass graft failure by intra-operative transit time flow measurement.** *Annals of Thoracic Surgery*. 86, 532-536, 2008.

13. Herman C, Sullivan JA, Buth K and Legare JF. **Intra-operative graft flow measurements during coronary artery bypass surgery predict in-hospital outcomes.** *Interactive CardioVascular and Thoracic Surgery*. 7, 582-585, 2008.

14. Balacumaraswami L, Abu-Omar Y, Selvanayagam J, Pigott D and Taggart DP. **The effects of on-pump and off-pump coronary artery bypass grafting on intra-operative graft flow in arterial and venous**

conduits defined by a flow/pressure ratio. *Journal of Thoracic and Cardiovascular Surgery*. 135, 533-539, 2008.

15. Tokuda Y, Song MH, Ueda Y, Usui A and Akita T. **Predicting early coronary artery bypass graft failure by intra-operative transit time flow measurement.** *Annals of Thoracic Surgery*. 84:1928-1933, 2007.

16. Balacumaraswami L and Taggart DP. **Intra-operative imaging techniques to assess coronary artery bypass graft patency.** *Annals of Thoracic Surgery*. 83, 2251-2257, 2007.

17. Di Giammarco G, Pano M, Cirmeni S, Pelini P, Vitolla G and Di Mauro M. **Predictive value of intra-operative transit-time flow measurement for short-term graft patency in coronary surgery.** *Journal of Thoracic and Cardiovascular Surgery*. 132, 468-474, 2006.

18. Gwozdziewicz M, Nemec P, Šimek M, Hajek R and Troubil M. **Sequential bypass grafting on the beating heart: blood flow characteristics.** *Annals of Thoracic Surgery*. 82, 620-623, 2006.

19. Kim KB, Kang CH and Lim C. **Prediction of graft flow impairment by intra-operative transit time flow measurement in off-pump coronary artery bypass using arterial grafts.** *Annals of Thoracic Surgery*. 80, 594-599, 2005.

20. Leong DK, Ashok V, Nishkantha A, Shan YH and Sim EK. **Transit-time flow measurement is essential in coronary artery bypass grafting.** *Annals of Thoracic Surgery*. 79, 854-857, 2005.

21. Kjaergard HK, Irmukhamedov A, Christensen JB and Schmidt TA. **Flow in coronary bypass conduits on-pump and off-pump.** *Annals of Thoracic Surgery*. 78, 2054-2056, 2004.

22. Gwozdziewicz M. **Cardiomed coronary flow meter for prevention of early occlusion in aortocoronary bypass grafting.** *Biomedical Papers*. 148, 59-61, 2004.

23. Walpoth BH, Mohadjer A, Gersbach P, Rogulenko R, Walpoth BN and Althaus U. **Intra-operative internal mammary artery transit-time flow measurements: comparative evaluation of two surgical pedicle preparation techniques.** *European Journal of Cardiothoracic Surgery*. 10(12), 1064-1068, 1996, discussion 1069-1070.

24. Laustsen J, Pedersen EM, Terp K, Steinbrüchel D, Kure HH, Paulsen PK, Jørgensen H and Paaske WP. **Validation of a new transit time ultrasound flowmeter in man.** *European Journal of Vascular and Endovascular Surgery*. 12(1), 91-96, 1996.

25 Walpoth BH, Bosshard A, Genyk I, Kipfer B, Berdat PA, Hess OM, Althaus U and Carrel TP. **Transit-time flow measurement for detection of early graft failure during myocardial revascularization.** *Annals of Thoracic Surgery*. 66(3), 1097-1100, 1998.

26. Albäck A, Roth WD, Ihlberg L, Biancari F and Lepäntalo M. **Pre-operative angiographic score and intra-operative flow as predictors of the mid-term patency of infrapopliteal bypass grafts.** *European Journal of Vascular and Endovascular Surgery*. 20(5), 447-453, 2000.

27 D'Ancona G, Karamanoukian HL, Salerno TA, Schmid S and Bergsland J. **Flow measurement in coronary surgery.** *Heart Surgery Forum*. 2(2), 121-124, 1999.

Appendix 3: Additional studies identified by the EAC

1. Desai ND, Miwa S, Kodama D, Koyama T, Cohen G, Pelletier MP, Cohen EA, Christakis GT, Goldman BS and Fremes SE. **A randomized comparison of intra-operative indocyanine green angiography and transit-time flow measurement to detect technical errors in coronary bypass grafts.** *Journal of Cardiovascular Surgery.* 132(3), 585-594, 2006, E-publication 28 July 2008.

2. Balacumaraswami L, Abu-Omar Y, Choudhary B, Pigott D and Taggart DP. **A comparison of transit time flowmetry and intra-operative fluorescence imaging for assessing coronary artery bypass graft patency.** *Journal of Thoracic and Cardiovascular Surgery.* 130(2), 315-320, 2005.

3. D'Ancona G, Karamanoukian HL, Salerno TA, Ricci M and Bergsland J. **Letter to the Editor - Flow measurement in coronary artery surgery.** *Annals of Thoracic Surgery.* 69, 1300-1301, 2000.

Appendix 4: Studies used to provide cost analysis data not identified by manufacturer's cost analysis literature search.

1. Kieser TM, Rose S, Kowalewski R and Belenkie I. **Transit-time flow predicts outcomes in coronary artery bypass graft patients: a series of 1000 consecutive arterial grafts.** *European Journal of Cardiothoracic Surgery*. 38, 155-162, 2010.

2. Becit N, Erkut B, Ceviz M, Unlu Y, Colak A and Kocak H. **The impact of intra-operative transit time flow measurements on the results of on-pump coronary surgery.** *European Journal of Cardiothoracic Surgery*. 32, 313-318, 2007.

3. Kim K-B, Kim JS, Kang H-J, Koo B-K, Kim H-S, Oh B-H and Park Y-B. **Ten-year experience with off-pump coronary artery bypass grafting: Lessons learned from early post-operative angiography.** *Journal of Thoracic and Cardiovascular Surgery*. 139, 256-262, 2010.

Appendix 5 Cost analysis tables

Table 1 Base case using the PQ probe (from Excel spread sheet)

Resource factor	CABG w/TTFM			CABG			Difference		
	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			9.79			0.00			9.79
Probes used	1.7	probes		0	probes		1.7	probes	
Probe cost			68.33			0.00			68.33
Cost of TTFM use per patient			**78.12**			**0.00**			**78.12**
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			10.41			0.00			10.41
Team cost of minor revision per patient			**0.24**			**0.00**			**0.24**
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			174.93			0.00			174.93
Team cost of major revision per patient			**7.52**			**0.00**			**7.52**
Sum of TTFM costs			**85.87**			**0.00**			**85.87**

Consequences of not doing TTFM					
Intra-operative 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 infection, rate	1.00%		1.00%	0.00%	
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**
Post-operative issues:					
Peri-operative MI, rate	0.00%		5.00%	-5.00%	
Peri-operative 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		**126.46**		**283.38**	**-156.92**

Table 2 Sensitivity Analysis when using the PQ probe

	Variable values					Delta Cost values, £			Width of interval
Variable	Best Case		Base Case	Worst Case		Best	Base	Worst	£
Duration of TTFM per procedure, min		2	2.35	5		-158.37	-156.92	-145.88	12.49
Mean No. of probes per procedure		1.4	1.7	2		-168.98	-156.92	-144.86	24.12
Rate of pats with revisions		2.20%	6.58%	14.60%		-162.08	-156.92	-147.47	14.61
Duration of minor revisions, min		2	2.5	5		-156.96	-156.92	-156.68	0.29
Duration of major revisions, min		27	42	57		-159.60	-156.92	-154.23	5.37
Relative rate of minor revisions		50.0 %	34.7 %	20.0 %		-158.57	-156.92	-155.32	3.25
Re-operative procedures, cost (£)		288.00	180.41	80.00		-156.92	-156.92	-156.92	0.00
Re-operative procedures, rates	0.6 %	8.5 %	3.0 %	8.5 %	0.6 %	-171.17	-156.92	-142.66	28.50
Deep sternal infection, cost (£)		1425.00	860.55	687.00		-156.92	-156.92	-156.92	0.00
Deep sternal infection, rates	0.0 %	5.5 %	1.0 %	5.5 %	0.0 %	-203.56	-156.92	-110.28	93.28
IABP, cost (£)		3346.00	2657.37	1968.00		-198.24	-156.92	-115.56	82.68
IABP, rates	0.0 %	13.9 %	1.0 %	3.5 %	3.5 %	-365.79	-156.92	2.52	368.31
MI, costs (£)		2067.00	1666.96	1267.00		-176.92	-156.92	-136.92	40.00
MI, rates	0.0 %	11.3 %	0.0 %	2.5 %	2.5 %	-261.60	-156.92	-79.86	181.74
Cost of CABG team composition, (£)		2.63	4.16	4.96		-163.37	-156.92	-153.58	9.79
On-pump rate		70.0 %	80.0 %	90.0 %		-156.98	-156.92	-156.86	0.12

Table 3. Base case with service and 250 day use a year

Resource factor V3 1582 service	CABG w/TTFM			CABG			Difference		
	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			9.79			0.00			9.79
Probes used	1.7	probes		0	probes		1.7	probes	
Probe cost			108.21			0.00			108.21
Cost of TTFM use per patient			**118.00**			**0.00**			**118.00**
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			10.41			0.00			10.41
Team cost of minor revision per patient			**0.24**			**0.00**			**0.24**
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			174.93			0.00			174.93
Team cost of major revision per patient			**7.52**			**0.00**			**7.52**
Sum of TTFM costs			**125.75**			**0.00**			**125.75**
Consequences of not doing TTFM									

Intra-operative 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 infection, rate	1.00%		1.00%	0.00%	
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**
Post-operative issues:					
Peri-operative MI, rate	0.00%		5.00%	-5.00%	
Peri-operative 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		**166.34**		**283.38**	**-117.04**

Table 4. Sensitivity analysis with service and 250 day use a year

	Variable values				Delta Cost values, £			Width of interval
Variable	Best Case	Base Case	Worst Case					£
Duration of TTFM per procedure, min	2	2.35	5		-118.49	-117.04	-106.00	12.49
Mean No. of probes per procedure	1.4	1.7	2		-136.13	-117.04	-97.94	38.19
Rate of pats with revisions	2.20%	6.58%	14.60%		-122.20	-117.04	-107.59	14.61
Duration of minor revisions, min	2	2.5	5		-117.08	-117.04	-116.80	0.29
Duration of major revisions, min	27	42	57		-119.72	-117.04	-114.35	5.37
Relative rate of minor revisions	50.0 %	34.7 %	20.0 %		-118.69	-117.04	-115.44	3.25
Re-operative procedures, cost (£)	288.00	180.41	80.00		-117.04	-117.04	-117.04	0.00
Re-operative procedures, rates	0.6 %	8.5 %	3.0 %	8.5 %	0.6 %	-131.29	-117.04	-102.78	28.50
Deep sternal infection, cost (£)	1425.00	860.55	687.00		-117.04	-117.04	-117.04	0.00
Deep sternal infection, rates	0.0 %	5.5 %	1.0 %	5.5 %	0.0 %	-163.68	-117.04	-70.40	93.28
IABP, cost (£)	3346.00	2657.37	1968.00		-158.36	-117.04	-75.68	82.68
IABP, rates	0.0 %	13.9 %	1.0 %	3.5 %	3.5 %	-325.91	-117.04	42.40	368.31
MI, costs (£)	2067.00	1666.96	1267.00		-137.04	-117.04	-97.04	40.00
MI, rates	0.0 %	11.3 %	0.0 %	2.5 %	2.5 %	-221.72	-117.04	-39.98	181.74
Cost of CABG team composition, (£)	2.63	4.16	4.96		-123.49	-117.04	-113.70	9.79
On-pump rate	70.0 %	80.0 %	90.0 %		-117.10	-117.04	-116.98	0.12