Australian Government

Medical Services Advisory Committee

Public Summary Document

Application No. 1354 – Intravascular Ultrasound (IVUS) Guided Coronary Stent Insertion

Applicant: **Boston Scientific**

Date of MSAC consideration: **MSAC 63rd Meeting, 1-2 April 2015**

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, see at www.msac.gov.au

1. Purpose of application and links to other applications

An application requesting MBS listing of intravascular ultrasound (IVUS)-guided coronary stent insertion for patients undergoing percutaneous coronary intervention (PCI) was received from Boston Scientific Pty Ltd by the Department of Health in September 2013.

2. MSAC's advice to the Minister

After considering the available evidence presented in relation to safety, clinical effectiveness and cost-effectiveness of intravascular ultrasound (IVUS)-guided coronary stent insertion, MSAC did not support public funding for IVUS-guided coronary stent insertion for patients undergoing percutaneous coronary intervention due to uncertain clinical effectiveness and uncertainty around the cost-effectiveness of the procedure.

3. Summary of consideration and rationale for MSAC's advice

MSAC noted that compared to angiography, IVUS may provide physicians with a better understanding of atherosclerotic vessels to determine appropriate treatment strategy, stent selection and implantation, and adequate deployment to restore blood flow. IVUS plays multiple roles in coronary stenting including determining suitability for stenting, guidance of stent selection and placement, and ensuring adequate stent deployment.

MSAC was concerned with differences between the clinical algorithm in the final submission and the clinical algorithm in the protocol provided by the Protocol Advisory Sub Committee (PASC), which increased level of clinical uncertainty. It was noted that the algorithm in the submission allows 'low/medium risk' patients to receive IVUS guidance. However, in the protocol, IVUS guidance was restricted to only 'high-risk' patients. Additionally, in the submission, both 'low/medium-risk' and 'high-risk' patients can receive simultaneous stent insertions at a subsequent occasion under guidance of angiography alone. This was not an option in the protocol. Evidence is lacking on the benefit of IVUS for coronary stent insertion

in 'low-risk' patients, which was acknowledged in the applicant's pre-MSAC response and stated support for restriction to 'high-risk' patients.

Due to lack of evidence no sub-group analysis was performed for the 'high-risk' patient groups, as defined in the protocol, in the submission. The applicant instead presented subgroup analysis for patients with acute coronary syndrome, diabetes and renal insufficiency, however; MSAC was concerned that this was not what the protocol mandated.

It was noted that there were no safety concerns identified, although MSAC was concerned that the safety analysis was not robust.

MSAC was concerned about the limited number of primary studies included in the analysis and the reliance on systematic reviews and meta-analyses, which do not allow assessment of the safety and efficacy of IVUS guidance for stent insertion of either bare metal stents (BMS) or drug-eluting stents (DES) for the types of 'high-risk' patients nominated in the protocol. Furthermore, stent technology is evolving with incomplete stent deployment now being less of a problem compared with earlier generation stents. It remains unclear, due to lack of research evidence, whether there is benefit of IVUS in percutaneous coronary intervention (PCI) stent insertion for naive patients compared to re-stenting procedures.

MSAC noted that there were small differences favouring IVUS. However the data were heterogeneous and therefore the 95% confidence intervals (CIs) approached 1. MSAC was concerned that there were no significant differences in important clinical outcomes such as myocardial infarctions (MIs) and mortality and that pooling of major adverse cardiac events (MACE) may be inappropriate. In addition, due to the short follow-up (2-3 years) in the clinical evidence base, it is not possible to assess whether the short-term benefits of IVUS are maintained over a longer period of time.

MSAC noted that a cost utility and cost-effectiveness analysis was performed with the modelled economic evaluation developed in two major steps: a trial-based evaluation (year 1) and extrapolation to a lifetime time horizon. MSAC was concerned, however, with the lack of evidence to support the lifetime time horizon of the model as the published data do not exceed 3 years and therefore, the lifetime benefits remain unknown. It was noted that the trial-based evaluation (year 1) discounted cost per QALY gained is estimated to be $166,462 for BMS and $489,868 for DES.

MSAC noted that a conservative uptake rate is assumed by the applicant, based on estimated procurement of IVUS capital equipment by hospitals. In addition, no changes in PBS costs are expected, although reductions in adverse events such as revascularisations and MIs could result in possible cost savings to the PBS in the form of reduced medications. MSAC considered this claim was uncertain as it was supported by evidence and thus claimed PBS savings were unlikely to be realised.

4. Background

In December 2001, MSAC considered evidence for IVUS both as a diagnostic tool and a therapeutic tool adjunct for interventional coronary procedures. MSAC did not recommend public funding for the service in that instance due to insufficient evidence of effectiveness and cost-effectiveness. The current submission pertains to evidence for IVUS as a therapeutic tool to assist coronary stent insertion. Use of IVUS as a diagnostic tool is not an intended purpose of the current submission.

5. Prerequisites to implementation of any funding advice

Several devices are currently listed on the Australian Register of Therapeutic Goods.

6. Proposal for public funding

The proposed schedule fee of $469.70 is based on MBS item 38241 – use of a coronary pressure wire during selective coronary angiography to measure fractional flow reserve and coronary flow reserve in one or more coronary artery or graft lesions (stenosis of 30–70%), to determine whether revascularisation should be performed where previous stress testing has either not been performed or the results are inconclusive. It is proposed that this item most closely resembles IVUS in complexity and time.

PASC suggested that the creation of two MBS items may be warranted:

- one item for the initial insertion of a stent under guidance of IVUS; and
- a second item for a subgroup of the population who will require insertion at a subsequent occasion under the guidance of IVUS.

The applicant proposed MBS item is:

Category 3 – Therapeutic Procedures
MBS XXXXX Selective Coronary Intravascular Ultrasound (IVUS), placement of IVUS catheter into the native coronary arteries, associated with the service to which item 38306 applies Multiple Services Rule (Anaes.) Fee: $469.70 Benefit: 75% = $352.30 85% = $399.25 [Relevant explanatory notes] Fee only payable when the service is provided in association with insertion of coronary stent/s (item 38306)

The proposed service is not expected to impact the natural growth in utilisation for coronary stent insertion.

7. Summary of Public Consultation Feedback/Consumer Issues

No consumer statement was provided in the assessment.

8. Proposed intervention's place in clinical management

Coronary angiography is well established in current Australian practice and is the most commonly used imaging modality to guide percutaneous coronary procedures.

The rationale for the use of IVUS at the time of stenting arises from limitations of coronary angiography in terms of assessing the severity of coronary stenosis in high-risk patients, as reflected in the final protocol.

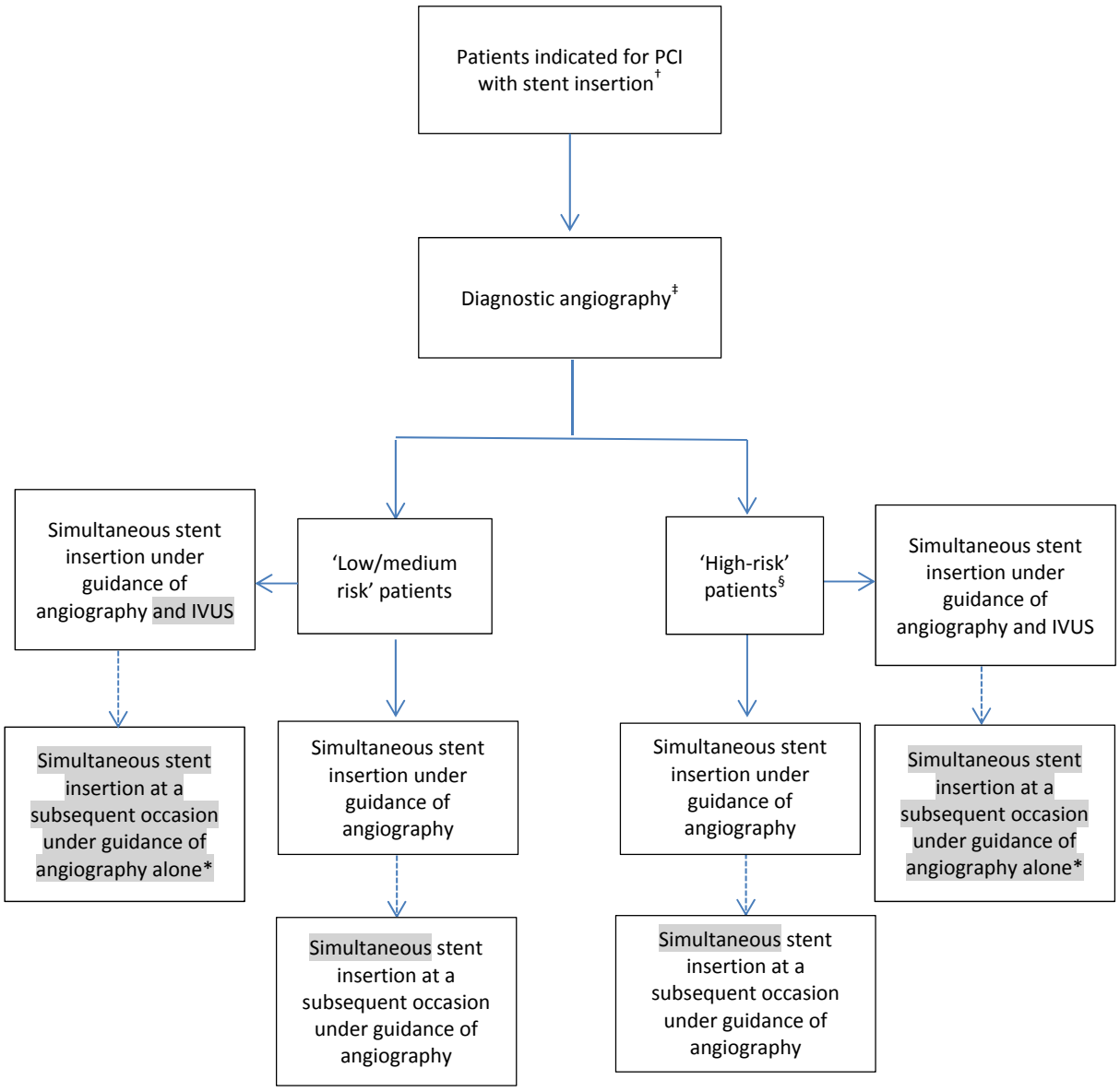
The proposed clinical management algorithm in the submission differed from the final Protocol in the following areas:

- It allows 'low/medium-risk' patients to receive IVUS guidance. However, the protocol restricted the use of IVUS guidance to 'high-risk' patients.

- It allows both 'low/medium-risk' patients and 'high-risk' patients to receive 'simultaneous stent insertion at a subsequent occasion under guidance of angiography alone' following 'simultaneous stent insertion under guidance of angiography and IVUS'.

These differences are illustrated below in figure 1.

Figure 1 – Proposed clinical algorithm for patients indicated for coronary stent insertion



† Patients with acute coronary syndrome – ST segment elevation myocardial infarction (STEMI), non-ST segment elevation myocardial infarction (NSTEMI) with higher risk of a cardiac event, unstable angina, stable angina who fail medical therapy or who have silent myocardial ischemia may be indicated for PCI/stenting as an elective, ad hoc or emergency procedure.
‡ Diagnostic angiography may be performed in addition to the functional assessments (e.g. fractional flow reserve) of coronary arteries.
§ 'High-risk' patients are identified based on their coronary anatomy, and the type and complexity of coronary lesions. They may include patients with coronary lesions that are intermediate in severity, especially when located in the left main coronary stem, patients undergoing complex coronary interventional procedures of ostial, coronary bifurcation, chronic total occlusions and lesions that are moderate to severely calcified, patients with challenging coronary anatomy, and patients who previously received a stent/s to identify underlying pathology for complications. 'High-risk' patients may also include those with comorbidities such as diabetes, renal insufficiency and acute coronary syndromes.
*Subsequent stent insertion of a previously stented lesion will not include the use of IVUS.
Source: Figure A.5-2 in the submission; subsequent changes made to the algorithm are highlighted.

In the applicant's pre-MSAC response the applicant stated support for restriction to 'high-risk' patients.

IVUS is the generic name for any ultrasound technology that is used to provide tomographic, 3-dimensional, 360-degree images from inside the lumen of a blood vessel. During PCI, IVUS may be used to assess the degree of narrowing in the coronary vessels in coronary artery disease (CAD). The technology may also be used to guide coronary stent insertion, particularly in cases of left main coronary artery stenting. IVUS guidance is used as an adjunct to angiography in performing stent insertion.

IVUS is not routinely used in Australia during percutaneous coronary stent insertion and is not listed on the MBS.

The intervention is proposed for patients eligible for coronary revascularisation undergoing percutaneous coronary intervention (PCI) with coronary stent insertion. Health Expert Standing Panel (HESP) clinical advice recommends limiting IVUS-guided percutaneous stent insertion to patients who are identified by their specialist as 'high-risk' based on their coronary anatomy, lesion type and complexity, and underlying comorbidities.

The 'high-risk' group may include patients with:

- intermediate left main coronary stenosis
- complex coronary lesions (e.g. ostial or bifurcation lesions, calcified lesions, chronic total occlusions)
- challenging coronary anatomy (e.g. coronary artery ectasia, giant coronary arteries, hazy coronary lesions)
- previous stents
- previous myocardial infarction (MI)
- acute coronary syndrome
- diabetes
- renal insufficiency.

Patients suitable for the procedure are identified through preliminary screening tests, such as an exercise stress tests and stress imaging studies. The majority of patients are diagnosed following an episode of angina and previous myocardial infarction. Coronary angiography is performed routinely in these patients to locate atherosclerotic lesions. It also provides guidance during percutaneous coronary intervention procedures.

On finding a lesion or narrowed coronary artery during diagnostic angiography, the cardiologist may proceed immediately to PCI. Procedural management involves balloon angioplasty, plaque modification procedures (such as cutting balloon or rotational atherectomy), and/or stenting. Angioplasty is performed by inserting a balloon catheter, which is directed, at the site of the lesion. The cardiologist inflates the balloon several times to restore blood flow to the heart. The cardiologist may place a stent during the procedure to keep the blood vessel open.

The rationale for the use of IVUS at the time of stenting arises from limitations of coronary angiography in terms of assessing the severity of coronary stenosis in 'high-risk' patients.

9. Comparator

The submission nominates coronary 'angiography alone' as the appropriate main comparator. However, the protocol is explicit that the comparator be coronary angiography without use of

IVUS (which in practical terms is the same, although may have allowed the use of other technologies such as optimal coherence tomography (OCT), which is only available in a few centres). Therefore, coronary angiography alone is an appropriate comparator.

Coronary angiography is well established in current Australian practice and is the most commonly used imaging modality to guide percutaneous coronary procedures. It is performed prior to percutaneous stent insertion to acquire diagnostic information to decide on the strategy for management. Patients who are indicated for, and consent to, PCI with stenting receive bare metal stents (BMS) or drug-eluting stents (DES) at the narrowed coronary artery segment to relieve the effects of myocardial ischemia and to improve symptoms and prognosis.

Comparators from the previous MSAC submission, 'PCI stent insertion without the use of IVUS (with or without another imaging modality)', are inappropriate because other imaging modalities, for example fractional flow reserve (FFR) and optical coherence tomography (OCT), are not always used in Australia when conducting PCI.

10. Comparative safety

No comparative harms of significance were identified in the Parise et al. (2011) or Ahn et al. (2014) meta-analyses.

Complications not reported as components of major adverse cardiac events (MACE) or mortality were infrequent and when they occurred were unlikely to be related to the additional use of the IVUS catheter. They were reported in five of the seven randomised controlled trials of BMS studies and one of the three randomised controlled trials of DES studies.

11. Comparative effectiveness

PASC agreed the Protocol should not pre-empt the restriction to subgroups before an analysis of the evidence is presented in the submission, but that where data permits, the clinical outcomes should be assessed separately for high risk subgroups, left main coronary artery (LMCA) disease and non LMCA disease. Due to lack of evidence no sub-group analysis was performed for the 'high-risk' patient groups, as defined in the protocol, in the submission. However, the applicant has presented subgroup analysis for patients with acute coronary syndrome, diabetes and renal insufficiency.

The clinical evidence presented in the assessment report is derived from two published meta-analyses, Parise et al. (2011) and Ahn et al. (2014). Overall, the meta-analyses report odds ratios in favour of IVUS guidance for rates of restenosis and revascularisation; however, the upper boundaries of the computed confidence intervals (CI) approach 1. The meta-analysis by Ahn et al. (2014) also found a favourable effect of IVUS in terms of major adverse cardiac events (MACE) and MI.

For studies included in the meta-analysis by Ahn et al. (2014), the patient populations would be considered 'high-risk' and therefore a subpopulation. Follow-up beyond six months was uncommon among the included studies and the durability of results beyond 2.5 years is unknown.

The clinical evidence base for BMS stents was based on the meta-analyses published by Parise et al. (2011). The applicant stated that:

> The primary evidence obtained from the Parise meta-analysis showed that IVUS-guided PCI in the pre–DES era improved acute procedural results (angiographic MLD) and thereby significantly reduced 6-month angiographic restenosis, 12-month revascularisation and MACE rates, supporting the use of IVUS guidance with BMS in patients with CAD. In this analysis, there was a neutral effect (e.g. neither positive nor negative) of IVUS guidance on MI or death over the follow-up of 6 months to 2.5 years.

The tables below reproduce the comparative efficacy outcomes.

Table 1: Results of the meta-analysis (Parise et al. 2011) for angiographic restenosis and rates of repeat revascularisation

Outcome	Intervention %	Comparator %	Odds ratio (95% CI)	Test of significance
Six month angiographic restenosis	12	29	0.64 (0.42–0.96) Favours IVUS	p=0.02
Rates of repeat revascularisation (TLR/TVR)	13	18	0.66 (0.48–0.91) Favours IVUS	p=0.004

Source: Table B.6-1, p. 88 of the assessment report.
CI=confidence interval; IVUS=intravascular ultrasound; TLR=target lesion revascularisation; TVR=target vessel revascularisation.

Table 2: Results of the meta-analysis (Parise et al. 2011) for MACE, MI and mortality

Outcome	Intervention %	Comparator %	Odds ratio (95% CI)	Test of significance
MACE*	19	23	*0.69 (0.49–0.97) favours IVUS or 0.72 (0.52–0.99) Favours IVUS)*	*p=0.044 or p=0.004*
MI	13	18	*0.67 (0.34–1.34)*	*p=0.51*
Mortality	2.4	1.6	*1.48 (0.81-2.69)*	*p=0.18*

Source: Table B.6-1, p. 88 of the assessment report/*populated during the evaluation.*
CI=confidence interval; MACE=major adverse cardiac events; MI=myocardial infarction.
**The odds ratio for MACE rate was presented differently in text and tables within the original publication and could not be verified; therefore, both estimates are presented.*

The assessment report does not address discrepancies in reporting within the meta-analysis or note that confidence intervals associated with the odds ratios generated by random and fixed effects models are wide with upper boundaries approaching 1 for several outcomes.

The results of the Parise et al. (2011) meta-analysis as they pertain to statements in the assessment report are as follows:

- For the protocol-specified primary endpoint of late stent thrombosis/restenosis, the meta-analysis found the odds ratio for 6-month angiographic restenosis, among six studies reporting this outcome, to be 0.64 (95% CI: 0.42-0.96) in favour of IVUS guidance. This supports the claim of improved 6-month angiographic restenosis with IVUS; however, it should be noted that the confidence interval approaches 1, indicating that the true population effect could be as much as patients with IVUS guidance being 58 per cent less likely to show 6-month angiographic restenosis or as little as 4 per cent less likely to show 6-month angiographic restenosis.

- The statement that 12-month revascularisation rates were significantly reduced with IVUS guidance as compared to angiography could not be validated. The included studies with follow-up ranging from 6 months to 2.5 years, and the majority of included studies, reported results at less than 1 year; therefore, no odds ratio for 12-month revascularisation rates was reported. Rather, the Parise et al. (2011) analysis largely utilised imputed 12-month repeat revascularisation rates based on the shape of Kaplan-Meier curves. The reported/imputed 12-month revascularisation rate odds ratio was given as 0.66 (95% CI: 0.48-0.91) in favour of IVUS. The odds ratio for revascularisation (reported not imputed) was presented differently in text and tables within the original publication and therefore could not be verified. The direction of effect associated with both reported odds ratios was in favour of IVUS guidance, and confidence intervals reported had lower and upper boundaries of between 0.46 and 0.91 respectively.
- The odds ratio for MACE rate was presented differently in text and tables within the original publication and therefore could not be verified. The direction of effect associated with both reported odds ratios was in favour of IVUS guidance. The odds ratio was reported as both 0.72 and 0.69 with confidence intervals with lower and upper boundaries of 0.52 to 0.99 and 0.49 and 0.97 respectively.
- The odds ratio for MI was 0.67 (95% CI: 0.34-1.34) and therefore is inconclusive.
- The odds ratio for death was 1.48 (95% CI: 0.81-2.69) and therefore is inconclusive.

The Parise et al. (2011) meta-analysis also conducted a sensitivity analysis by removing the SIPS trial because this trial contained patients who did not receive stenting as a therapy. No change in direction of effect was observed.

The assessment report presents the results of meta-analyses published by Ahn et al. (2014) of IVUS guidance compared to angiography for DES. Additionally, the assessment report presents results of a meta-analysis conducted by the applicant using only the RCT evidence for studies using DES.

The assessment report states that:

> The meta-analyses by Ahn and colleagues showed that IVUS guidance for PCI was associated with a significantly reduced risk of death, MI, ST, and target lesion revascularisation (TLR) – as well as a lower risk of the composite of death, MI, or repeated revascularisation (MACE) – over a follow-up period of 12 months to 4 years.

The assessment report also presents the results of a meta-analysis done using only data from the three RCTs. In the summary of these meta-analyses, the assessment report concludes that, compared to angiographic-guided PCI, IVUS-guided PCI was associated with a reduced risk of mortality, TLR and target vessel revascularisation (TVR), and MI.

The results of the meta-analyses as they pertain to outcomes specified in the protocol are presented in the tables below.

Table 3: Results of the meta-analyses (Ahn et al. 2014 and the assessment report) for angiographic restenosis and rates of repeat revascularisation

Outcome	Odds ratio (95% CI)	Test of significance
Ahn et al. (2014) Rates of repeat TLR	0.81 (0.66-1.0)	p=0.046
Ahn et al. (2014) Rates of repeat revascularisation TVR	0.82 (0.70-0.97) Favours IVUS	p=0.022
Ahn et al. (2014) Stent thrombosis	0.59 (0.47–*0.75)* Favours IVUS	p<0.001
RCTs only TLR/TVR	0.62 (0.39-1.00)	NR

Source: Table B.6-1, p.88 of the assessment report/Figures B.6-1 to B.6-3 of the assessment report, pp.89–91.
CI=confidence interval; IVUS=intravascular ultrasound; NR=not reported; TLR=target lesion revascularisation; TVR=target vessel revascularisation.

Table 4: Results of the meta-analysis (Ahn et al. 2014 and the assessment report) for MACE, MI and Mortality

Outcome	Odds ratio (95% CI)	Test of significance
Ahn et al. (2014) MACE	0.74 (0.64-0.85) Favours IVUS	p<0.001
RCTs only MACE	NR	NR
Ahn et al. (2014) MI	0.57 (0.44–0.75) Favours IVUS	p<0.001
The assessment report MI	0.63 (0.29–1.39)	NR
Ahn et al. (2014) Mortality	0.61 (0.48-0.79) Favours IVUS	p<0.001
The assessment report Mortality	0.71 (0.18–2.88)	NR

Source: Table B.6-1, p.88 of the assessment report/Figures B.6-1 to B.6-3 of the assessment report, pp.89–91.
IVUS=intravascular ultrasound; MACE=major adverse cardiac events; MI=myocardial infarction; NR=not reported.

12. Economic evaluation

The assessment report presents a stepped economic evaluation, based on systematic reviews and implementing a modelled evaluation using variables reported in Section C studies. The economic evaluation presented in the assessment does not follow the PICO outlined in the protocol.

The protocol noted that given the chronic nature of the condition under study and the impact of patient attributes on the model output, an individual-based model is recommended. Two extended PICOs [were] proposed: the first for patients undergoing initial stent placement; the second for patients requiring re-stenting or other interventions following a complication or failure of the initial stent.

The applicant noted in the assessment report that patients who have been previously stented are at a higher risk of adverse events, therefore it is necessary for results of the economic evaluation to be interpreted separately for this patient group. However, none of the clinical studies included in the systematic reviews in section B presented results comparing the efficacy of IVUS for treatment naïve or repeat stent insertion patients.

The assessment report details five economic evaluations, but deems them inappropriate for use in the current evaluation. No cost-effectiveness studies were reported as presenting a lifetime time horizon to evaluate the overall cost-effectiveness of IVUS use in the population.

A cost-utility and cost-effectiveness analysis was performed to assess the incremental cost of coronary stent insertion guided by IVUS and angiography compared to the insertion guided by angiography alone per extra unit of health outcome achieved (e.g. life year gained (LYG) and quality adjusted life years (QALY) gained). The economic evaluation was conducted using Excel 2010. Markov models for IVUS-guided BMS and DES using systematic reviews by Parise et al. (2011) for BMS and Ahn et al. (2014) for DES. These publications provide the OR estimates for revascularisation (TLR/TVR) and MI. The models include event-free, MI, TLR/TVR, and background mortality (referred to as normal mortality).

The modelled economic evaluation has been developed in two major steps: a trial-based evaluation (Year 1), and extrapolation to a lifetime time horizon. Each step presents an incremental cost-effectiveness ratio (ICER) of the insertion guided by IVUS plus angiography relative to that by angiography alone. Table 5 and Table 6 below summarise the results of the economic evaluation of the proposed intervention. Table 5 provides the results of the Step 1 economic evaluation. The results are presented as the incremental cost per QALY gained, and the costs and benefits are discounted. The discounted cost per QALY gained is estimated to be $166,462 in the case of BMS, and $489,868 for DES. The ICERs are higher in Step 1 than those obtained in the life cycle (Step 2) scenario, since the costs associated with IVUS all occur in the initial cycle.

Table 5: Step 1 - Year 1 (trial) results of the economic evaluation

Resource item description	IVUS	Angio.	Incremental
Step 1: Trial-based model evaluation			
IVUS-guided BMS implantation analysis			
Cost	$15,606.78	$14,717.21	$925.83
Effect (LYs)	0.968	0.966	0.002
		Cost per LYG	$411,792.45
Effect (QALYs)	0.801	0.795	0.005
		Cost per QALY gained	$166,462.01
		Upper 95% CL of differences in outcome	*Dominated*
		Lower 95% CL of differences in outcome	*$49,990.14*
IVUS-guided DES implantation analysis			
Cost	$17,137.05	$15,686.99	$1,450.06
Effect (LYs)	0.969	0.968	0.001
		Cost per LYG	$1,002,426.09
Effect (QALYs)	0.816	0.813	0.003
		Cost per QALY gained	$489,868.31

Resource item description	IVUS	Angio.	Incremental
		Upper 95% CL of differences in outcome	*$1,038,632.26*
		Lower 95% CL of differences in outcome	*$325,841.40*

Source: Assessment report, p. 127, Table 5.4. Angio=angiography only; BMS=bare metal stents; CL=confidence limit; DES=drug-eluting stent; IVUS=intravascular ultrasound; LYs=life years; LYG=life year gained; QALYs=quality adjusted life years. Confidence limits taken from spreadsheet during critique.

The applicant noted in the assessment report that extrapolation is appropriate because the majority of the costs of IVUS are incurred in the first year, and benefits occur in the future.

Table 6: Step 2 - lifetime results of the economic evaluation

Resource item description	IVUS	Angio.	Incremental
IVUS-guided BMS implantation analysis			
Cost per LYG – lifetime; base case			
Cost	$19,392.14	$20,454.62	($1,026.48)
Effect (LYs)	13.742	13.607	0.135
		Cost per LYG	($7,861.72)
Cost per QALY gained – lifetime; base case			
Effect (QALYs)	11.169	11.044	0.124
		Cost per QALY gained	($8,555.62)
		Upper 95% CL of differences in outcome	*Dominated*
		Lower 95% CL of differences in outcome	*Dominant*
IVUS-guided DES implantation analysis			
Cost per LYG – lifetime; base case			
Cost	$22,598.12	$23,252.54	($654.42)
Effect (LYs)	12.932	12.742	0.190
		Cost per LYG	($3,439.87)
Cost per QALY gained – lifetime; base case			
Effect (QALYs)	10.619	10.442	0.176
		Cost per QALY gained	($3,717.32)
		Upper 95% CL of differences in outcome	*$6,183.98*
		Lower 95% CL of differences in outcome	*Dominant*

Source: Assessment report, p. 126, Table 5.3. Angio=angiography only; BMS=bare metal stents; CL=confidence limit; DES=drug-eluting stent; IVUS=intravascular ultrasound; LYs=life years; LYG=life year gained; QALYs=quality adjusted life years. Confidence limits taken from spreadsheet during critique.

A supplementary analysis was presented in the SBA in which benefits of IVUS use would cease at 3 years while the time horizon of the evaluation still covers the lifetime of the cohort generated ICERs of $2,600 per LYG and $2,900 per QALY gained for BMS implantation and $3,100 per LYG and $3,400 per QALY gained for DES implantation analyses. These estimates are higher than the final ICER of the base-case scenario, but lower than the ICERs generated from the trial-based evaluation.

13. Financial/budgetary impacts

Financial implications are noted in the assessment report as being estimated using an epidemiologic approach, first estimating the disease burden of CAD in Australia, and then determining the financial implications to the MBS and broader health system. The number of patients receiving IVUS is derived from patients receiving stent insertion, classified as MBS item 38306. Using data from 2010 to 2013, a linear regression is used in the assessment report for projection until 2019. Estimation of uptake hinges on the assumption that an additional 20 IVUS machines will be purchased in conjunction with the current stock of 52 machines.

A conservative uptake rate is assumed by the applicant, based on estimated procurement of IVUS capital equipment by hospitals. Procurement of an additional 20 IVUS systems on top of the current 53 systems in operation would result in approximately 1,275 IVUS-guided procedures in 2015, increasing to 7,010 by 2019. A sensitivity analysis was conducted which included a high uptake rate and analysis of the high-risk patient group.

The assessment report states that no changes in costs to the PBS are expected as IVUS is an additional therapy, but further notes that by reducing adverse events, such as revascularisations and MIs, it can be expected that there will be a cost savings to the PBS in the form of reduced medications.

14. Key issues from ESC for MSAC

ESC noted that the SBA deviated from the patient population stated in the Protocol ('high-risk' patients), to include low and medium risk patients. ESC discussed how this had increased the level of uncertainty regarding clinical efficacy and also the financial impact on the MBS.

ESC considered current MBS data for the comparator, but noted that this could not identify how many patients were in the 'high-risk' category. Due to this limitation, ESC could not estimate the number of patients likely to receive the proposed service. However, it was noted that cardiac specialist estimates have been as high as 60%.

ESC noted that IVUS is now used in some clinical cases. Typical applications include,

- as a diagnostic approach for patients with a normal angiogram after ACS;
- eccentric lesions where the length is important for determining the size and length of the stent; and
- clinical concern for dissection.

ESC noted PASC's suggestion that the creation of two MBS items may be warranted – one item for the initial insertion of a stent under guidance of IVUS, and a second item for a subgroup of the population who will require insertion at a subsequent occasion under the guidance of IVUS. ESC did not form an agreed approach on this matter and therefore referred the issue to MSAC to consider as part of its deliberations.

ESC concluded that the data quality for clinical efficacy is poor, based on meta-analyses rather than well-powered clinical trials. The true extent of the efficacy of IVUS therefore remained uncertain and ESC determined that the claim of clinical benefits may not be supported. Due to the lack of research evidence, the benefit of IVUS in PCI stent insertion for naive compared with re-stenting procedures could not be assessed by ESC and remained unclear.

ESC also noted that the literature for BMS was likely based on first generation technology for stents and angiographic practice that has changed or is no longer in use.

ESC noted expert advice that there may be a clinical need for the addition of second stent insertion procedure after initial IVUS and stent use.

The reliance on clinical evidence as presented in the systematic reviews did not allow ESC to make an assessment of the safety and efficacy of IVUS guidance for stent insertion of either BMS or DES for the types of high-risk patients nominated in the protocol. ESC agreed that this limitation may have been mitigated if the applicant utilised the primary evidence base and, in the case of DES, utilised the observational as well as the RCT evidence. The benefit of IVUS guidance for stent insertion in 'high-risk' patients is unclear.

As the time horizon for trial data was short at 2-3 years, there were concerns about the accuracy of the extrapolation to 20 years in the economic model.

ESC discussed the pooled data used for the meta-analysis, which consisted of three main studies and a few observational studies. ESC concluded that the differing outcomes of the studies resulted in heterogeneity and that the observational studies had patient selection biases.

ESC noted that there were issues with the quality of the meta-analyses that may result in the effects of these studies being unreliable. These issues include: wide confidence intervals, often close to unity, heterogeneity in populations, large reliance on observational data for drug eluting stents and inadequate follow-up duration to assess beyond short-term benefits.

ESC agreed that the applicant's estimate of an additional 20 machines being purchased if MBS funding is available for the service was likely an underestimate. This was based on the understanding that the costs of procurement would not be high compared to the benefit of MBS funding.

The financial impact of listing IVUS guidance is unclear due to uncertainty about:

- the number of patients who will receive the service;
- limited data on the number of 'high-risk' patients in Australia;
- the broadening of the clinical algorithm to include IVUS guided stent insertion for 'low/medium-risk' patients; and
- the effect of the number of available IVUS systems if MBS funding commences.

ESC noted that it is unclear how diffused IVUS is in the Australian public/private sector at present. There was uncertainty about the time and level of take-up in the future if this service is funded through the MBS.

15. Other significant factors

Nil

16. Applicant's comments on MSAC's Public Summary Document

Boston Scientific is disappointed with the outcome of this re-submission. We support a restricted listing for IVUS-guided stent placement in a patient population of high-risk patients in whom this service is most frequently used in current clinical practice.

We note that IVUS-guided stent placement is not a new technology and the clinical evidence has evolved overtime: the pivotal evidence presented for IVUS-guided drug eluting stent placement is a meta-analysis of 26,503 patients from independent studies (12,499 treated with IVUS and 14,004 with angiography alone), and IVUS-guided stent placement demonstrated significantly reduced revascularisation, myocardial infarction and cardiac death. As mentioned in previous correspondence, we acknowledge that the published evidence does not pertain to the specific high-risk subgroups of patients identified by the HESP. However, the benefit of IVUS increases in studies where subgroup analysis is available. This is compelling real world evidence that IVUS-guided stent placement improves long term health outcomes. It is unlikely that primary evidence in the specific high-risk population identified by HESP will emerge at any time in the foreseeable future.

17. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website at: www.msac.gov.au.