NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Health Technology Appraisal

Drug-eluting stents for the treatment of coronary heart disease

Responses to consultee and commentator comments on the ACD

Consultee and Commentator	Section	Comment	Institute's response
Abbott Laboratories Ltd		Abbott acknowledges and supports all the statements and objections made in the British Cardiac Industry Association (BCIA) submission. In addition we would like to express our concern for patients with cardiovascular disease for whom access to treatment might be adversely affected by a final appraisal decision based upon insufficient independent clinically robust data and contemporary pricing practice. Our concerns are as follows: **Has all the evidence been taken into account? Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence and are the preliminary views on the resource impact and implications for the NHS appropriate?**	Comments noted. See responses to BCIA comments below.
Abbott Laboratories		Clinical data referenced to Randomised Controlled Trials	The Appraisal Committee considered BCIS's

Ltd		We support the comprehensively referenced data that British Cardiac Interventional Society (BCIS) have previously submitted to define the endpoints, including: Bare Metal Stent (BMS) Absolute Revascularisation Risk of 13% taken from the Scottish registry prior to DES (year 2000-2001, Pell & Slack 2004). In addition if the data takes into consideration the relative number of patients with acute and non acute coronary syndromes to define the absolute risk of revascularization for the unselected population it is 14.5%. Relative Risk for the following independent risk factors: Small Vessels 1.75, Long Lesions 1.35, Diabetes 1.52. This would lead to a Risk Reduction gain from DES of: 69% Small Vessels, 70% Long Lesions, 61% Diabetes. Using a price delta of £300 between DES and BMS, which reflects current UK market prices. We would advise that the Appraisal Committee insists that data derived from Randomised Controlled Trials (RCT) is used in the modelling as this follows the Institute's own Guide to the Methods of Technology Appraisal (section 3.2.2.1), which states ".....RCTs are therefore ranked first in the hierarchy of evidence for measures of relative treatment effect." If the Appraisal Committee deviates from this we would like to understand why.	assumptions; see FAD sections 4.2.23, 4.2.28, 4.3.13 and 4.3.14. See FAD section 4.3.6 and 4.3.7 for the Appraisal Committee's considerations.
Abbott Laboratories Ltd		<u>Deviation from modelling data used in 2003 guidance</u> We question why the current appraisal deviates from the clinical data that formed the basis for the October 2003 guidance in terms of Absolute Risk of 12.7% & Risk Reduction of 79% and which is supported by a growing body of	This is a part review of technology appraisal no.71, all data relevant to the previous appraisal and additional data have been

		Randomised Controlled Trial data. By making unreferenced or unsupported changes the appraisal would be suggesting that the model used in the previous guidance was not robust. The use of RCT data combined with the reality of a lowering price delta between Drug Eluting and Bare Metal Stents would have a significant impact, and shows DES to be more cost-effective than 4 years ago when the original guidance was issued. We would appreciate the references for the trials used to define the risks in the current appraisal and to understand why these have been selected in preference to the data in the 2003 model as well as a read only copy of the economic model.	included in this review. The assessment report provides details on all trials included in the systematic review.
Abbott Laboratories Ltd		<u>Use of contemporary data</u> Due to the length of time this appraisal has taken, (the original submission was made in 2006) reliable trial data and pricing information from the last 2 years are not included. The SPIRIT III trial compares the Xience V Everolimus eluting stent to the Taxus stent and is the first RCT, which shows clinical superiority of one DES over another on the clinical end point of MACE (major adverse clinical event). The Xience V stent is on the VISION chromium cobalt BMS platform, which is sited by LRiG for having low restenosis rates in the Basket trial. It should therefore be important to look at the risk reduction and cost effectiveness of second generation DES, which due to the timing this appraisal has been unable to do.	Comments noted. The Institute has received data from PASA for 2007/08; see FAD section 3.6. See FAD section 4.3.3 for the Appraisal Committee's consideration of the comparisons between different types of DESs.
Abbott Laboratories Ltd		**<u>Are the provisional recommendations of the Appraisal Committee sound and constitute a suitable basis for the preparation of guidance to the NHS?</u>**	

		<u>Comprehensive Clinical and Budget Impact and Patient Choice</u> Abbott is of opinion that the present appraisal has not considered the true impact of withdrawing DES as a treatment option in the UK. There has been an assumption that the use of BMS and DES are interchangeable, when this is clearly not the case. A significant number of patients will not get the best clinical outcome from a BMS procedure and would receive more invasive and expensive Coronary Artery Bypass Graft (CABG) surgery in the absence of DES. The true budget, logistical and social impact of this transfer of treatment was not considered, neither the patients loss of choice to receive a more conservative treatment. The BCIS audit data has reported procedure numbers for England and Wales as 58,576 for 2005, we have seen 11% growth during 2006 and 9% growth in 2007 leading to over 70,000 procedures being carried out in 2007. The last reported CABG figures were 22,724 procedures, so a switch of patients from PCI to Surgery with longer procedure times and the increased patient stay, would impact on surgical capacity and bed availability. This would be expected to lead to unacceptable waiting periods for patients, probably exceeding the Government recommendation of less than 18 weeks. The NHS does not have the capacity to provide sufficient alternative treatment to PCI with significantly curtailed DES usage.	DESs are recommended in circumstances outlined in FAD section 1.1.
Abbott Laboratories Ltd		<u>Code of Practice for Declaring and Dealing with Conflicts of Interest</u> In the Code of Practice for Declaring and Dealing with Conflicts of Interest published by NICE in April 2007, section 3.5 states if: A personal non-pecuniary interest in a topic under consideration might include, but is not limited to:	Comment noted. The Assessment Group began working on this appraisal in 2005 therefore the Code of Practice for Declaring and Dealing with Conflicts of Interest does not apply

		a clear opinion, reached as the conclusion of a research project, about the clinical and/or cost effectiveness of an intervention under review a public statement in which an individual covered by this Code has expressed a clear opinion about the matter under consideration, which could reasonably be interpreted as prejudicial to an objective interpretation of the evidence As such we consider that the prior publication by Professor Bagust and Professor Walley in the Jan 2006 issue of The Heart on cost effectiveness of coronary artery stenting in a UK setting, contravenes this code.	to this appraisal. Previously the Institute has assessed the situation and concluded that there was no conflict of interest.
Abbott Laboratories Ltd		The body of clinical evidence supporting the safety and effectiveness of drug-eluting stents for treating patients with diseased coronary arteries and chest pain is vast and growing. Drug-eluting stents were designed to reduce vessel renarrowing and to treat chest pain, which they have proven to do. Limiting reimbursement for drug-eluting stenting would reduce patient access to an important treatment option and increase the number of re-interventions or major open heart surgery that patients would undergo.	DESs are recommended in circumstances outlined in FAD section 1.1.
Abbott Laboratories Ltd		Abbott will not support a NICE drug-eluting stent reimbursement recommendation based on non-randomised data from only one treatment center in the UK. Abbott would support a determination based on the most recent randomised clinical trial data available, taking into account the outcomes of patients treated with drug eluting stents across a broad sampling of physicians and treatment centers. We therefore call for the appraisal to be restarted with an independent economic modelling group employing the most up to date clinical and pricing data. We would be concerned by a referral to the Decision Support Unit as this will be starting from the premise of reviewing the existing LRiG model which we believe	DESs are recommended in circumstances outlined in FAD section 1.1. The Appraisal Committee did not accept all parameters and assumptions in LRiGs model; see FAD sections 4.3.4, 4.3.5, 4.3.6, 4.3.7,

		is inherently biased.	4.3.10, 4.3.11, 4.3.12, 4.3.13 and 4.3.14. The Appraisal Committee considered BCIS's assumptions; see FAD sections 4.2.23, 4.2.28, 4.3.13 and 4.3.14.
Boston Scientific		Boston Scientific fundamentally disagrees with the draft guidance contained within the ACD for TA71 and the basis upon which this has been prepared. The methodology used is contrary to the Institute's own procedures and the conclusions drawn regarding cost-effectiveness are based on an inappropriate and unscientific selection of a limited part of the evidence base, disregarding other important data. The Liverpool Reviews and implementation Group (LRiG), who has acted as the Assessment Group (AG) for the purposes of this appraisal, has an important conflict of interest as a result of its own controversial research in this area and this has prevented an impartial review of the evidence. Moreover, neither the Assessment Report nor NICE's papers contain any formal declaration of such interest (as required under NICE's procedures) and there is no indication that this was recognised and considered in any way by the Appraisal Committee. In these circumstances, we believe it is inappropriate to place any reliance whatsoever upon the Assessment Report prepared by LRiG or to proceed with the ACD based upon that Report in that it is likely to produce a perverse outcome. In this response we will also explain why the consequences of applying the draft guidance proposed in the ACD would be detrimental to patient care and would have a negative impact on NHS services.	DESs are recommended in circumstances outlined in FAD section 1.1. The Appraisal Committee did not accept all parameters and assumptions in LRiGs model see FAD sections 4.3.4, 4.3.5, 4.3.6, 4.3.7, 4.3.10, 4.3.11, 4.3.12, 4.3.13 and 4.3.14. The Appraisal Committee considered BCIS's assumptions; see FAD sections 4.2.23, 4.2.28, 4.3.13 and 4.3.14.

Boston Scientific		1. **<u>Failure to follow the appraisal methodology set out on the Institute's *Guide to the Technology Appraisal Process*</u>** **Hierarchy of evidence** In the Institute's 'Guide to the Methods of Technology Appraisal', page 11, paragraphs 3.2.2.1 and 3.2.2.2 (emphasis added) "…***RCTs are therefore ranked first in the hierarchy of evidence*** *for measures of relative treatment effect."* and *"The Institute has a strong preference for evidence from 'head-to-head' RCTs that directly compare the technology and the appropriate comparator.* ***Wherever such evidence is available and includes relevant outcome evidence, this is preferred over other study designs.****"*	See section FAD 4.3.6 and 4.3.7 for the Appraisal Committee's considerations.
Boston Scientific		**The reference case** In the Institute's 'Guide to the Methods of Technology Appraisal', page 20, paragraph 5.3.1.1 "*The Institute has to make decisions across different technologies and disease areas. It is, therefore, important that analyses of clinical and cost effectiveness undertaken to inform the appraisal adopt a* ***consistent approach****. To facilitate this, the Institute has defined a '****reference case'*** *that specifies the methods considered by the Institute to be the most appropriate for the Appraisal Committee's purpose and consistent with an NHS objective of maximising health gain from limited resources.."* The reference case requests that **all evidence on outcomes should be obtained from a systematic review** from which results will be most valid if they are based on evidence from head-to-head RCTs. ***Only when such evidence is not available***, other sources of comparison such as indirect trial comparisons	See FAD section 4.3.6 and 4.3.7 for the Appraisal Committee's considerations.

		and non-RCT evidence can be used. However the potential selection bias should be assessed in an analysis of uncertainty.	
Boston Scientific		**Evidence considered in the ACD** As a product class DES are arguably the most researched product in the history of medical devices. Boston Scientific has itself developed the extensive TAXUS clinical programme, a comprehensive series of RCTs dealing with increasingly complex lesions over time and reporting outcomes over a series of time points. These results have consistently shown the benefits of Taxus over the BMS comparator and have been provided to the Institute as part of previous submissions and as separate 'for information' communications. Overall the AG identified 17 RCTs comparing DES to Bare Metal Stents (BMS). The clinical effectiveness conclusions were based on RCTs and clearly show the benefit of DES over BMS in reducing the need for revascularization. The clinical evaluation considers RCTs as they are the best sources of evidence available to evaluate the efficacy and safety of DES vs. BMS. No observational studies were included as no studies of sufficient quality and relevance have been published. **However the cost-effectiveness results are not based on a systematic review of the available RCTs.** The initial analysis from the AG was not based on the extensive RCT data available in relation to DES, but instead relied on the Liverpool Cardiothoracic Centre (CTC) database: a single-centre non randomized audit. The fundamental flaws in this approach were summarised by Boston Scientific in our response of 12 January 2007 to the Assessment Report and were also identified by other consultees and commentators at that stage. Drug eluting stents have been and continue to be extensively researched. Each clinical programme has certain characteristics that can strengthen or weaken its	See FAD section 4.3.6 and 4.3.7 for the Committee's considerations. DESs are recommended in circumstances outlined in FAD section 1.1. The Appraisal Committee was aware of the views expressed by consultees and commentators about the CTC database. Therefore it did not accept all parameters and assumptions in LRiGs model see FAD sections 4.3.4, 4.3.5, 4.3.6, 4.3.7, 4.3.10, 4.3.11, 4.3.12, 4.3.13 and 4.3.14. The Appraisal Committee considered BCIS's assumptions see FAD sections 4.2.23, 4.2.28, 4.3.13 and 4.3.14.

		value in terms of evidence. Choosing which data to use for a given analysis should include a determination of the "level of evidence" for each trial used in a data set. An industry standard has been developed to categorize individual clinical programs based on their "Level of Evidence Score."[i] When applying industry standards for evidence to clinical studies like BASKET or the CTC database it becomes very clear that these studies have very low levels of evidence scores. In considering the evidence for the purposes of the ACD, the Appraisal Committee has moved away from the CTC database as the sole source of information, however its recommendations are still not based on a comprehensive review of the literature but rather material that is highly selected in a way that is not consistent with the ranking of evidence provided under NICE's procedures and is unrepresentative of the data as a whole. The evidence relied upon by the Committee for these purposes is limited to the results of a single-centre RCT from Switzerland (the BASKET study), the Scottish registry, comments from clinical specialists advising the Committee as well material collected for the Liverpool CTC database. The exclusion of other relevant data from consideration by the Committee means that the conclusions set out in the ACD are unreliable.	
Boston Scientific		In summary, our objections to the approach to the evidence for the assessment of cost effectiveness in the ACD are as follows: 1. *The conclusions in the ACD are based on the controversial methodology used by the Assessment Group* The conclusions reached by the Appraisal Committee are based on a	Comments noted. The Appraisal Committee was aware of the views expressed by consultees and commentators about the CTC database. Therefore it did not accept

		novel approach developed by the Assessment Group, which is not generally accepted or standard methodology and which we believe to be substantially flawed, The LRiG approach involves the application of efficacy data from RCTs to patient data collected from the Liverpool CTC for the purposes of a database (which was uncontrolled and included only patients treated with BMS and not any DES patients) in an attempt to reach conclusions about the effectiveness of DES in a "real world" setting. There is no attempt to investigate whether the population of patients treated with BMS in the Liverpool CTC are properly comparable with those treated with DES at other centres. The fundamental principle underlying this strategy (i.e. whether efficacy data from RCTs may be transposed in this way) is untested and the fact that the conclusions of the Assessment Group in this case are substantially different not only from the conclusions of consultees to this appraisal, but also to the conclusions of published assessments of cost effectiveness (with the exception of those published by the Assessment Group) suggests that it is not a valid approach. We believe that the use of a novel and untested strategy to assess cost effectiveness forms an inappropriate basis for decisions on the availability of treatments for NHS patients. Instead cost effectiveness of DES may be considered reliably only by assessing patients treated with such products.	all parameters and assumptions in LRiGs model see FAD sections 4.3.4, 4.3.5, 4.3.6, 4.3.7, 4.3.10, 4.3.11, 4.3.12, 4.3.13 and 4.3.14. The Appraisal Committee considered BCIS's assumptions see FAD sections 4.2.23, 4.2.28, 4.3.13 and 4.3.14.
Boston Scientific		2. *The fact that the Appraisal Committee has based its conclusions almost entirely on data from BASKET and the Liverpool CTC introduces biases to the assessment.* In the ACD, the Appraisal Committee rely:	DESs are recommended in circumstances outlined in FAD section 1.1. The Appraisal Committee was aware of the views

		• on the BASKET study for the purposes of its estimates of: the absolute rate of revascularisation (paragraph 4.3.6) • on the reduction in the relative risk of revascularization rate (4.3.7): appear to have taken an arbitrary number that is not derived from a meta-analysis • on the Liverpool CTC database for the purposes of its estimates of: (a) the number of stents used for each of the various risk groups (paragraph 4.3.8) and (b) the incidence of risk factors (long lesions, small vessels). The BASKET study is a single centre study conducted in a non-UK population. Furthermore the authors comment that patients refused to consent to participate in the study in cases where the referring physician had expressed a preference for DES, which may suggest that trial participants were perceived to be at lower risk of revascularisation and the fact that the revascularisation rates reported are lower than those elsewhere is likely to be attributable, at least in part, to recruitment bias. The Liverpool CTC database is another single centre data source, in this case derived from unrandomised treatment allocation. As a single centre, there is no proper basis for a belief that it is representative of NHS experience across England and Wales as a whole and no attempt has been made to investigate whether differences exist. Furthermore, the fact that the treatment is unrandomised, means that the data generated are likely to be influenced by biases and are therefore inherently unreliable. The Appraisal Committee has accepted that the initial conclusions of the Assessment Group with respect to risk factors, which were based on	expressed by consultees and commentators about the CTC database. Therefore it did not accept all the parameters and assumptions in LRiGs model see FAD sections 4.3.4, 4.3.5, 4.3.6, 4.3.7, 4.3.10, 4.3.11, 4.3.12, 4.3.13 and 4.3.14. The Appraisal Committee considered BCIS's assumptions see FAD sections 4.2.23, 4.2.28, 4.3.13 and 4.3.14.

		the Liverpool CTC data, were incorrect. However, despite accepting this deficiency of the CTC database, the Appraisal Committee has still chosen to rely on the database - even to the extent of using the non-significant figures for risk factors, Boston Scientific believes that the decision to rely on these single centre data sources, rather than the very extensive data available from RCTs, lacks scientific credibility and is contrary to NICE methodology.	
Boston Scientific		3. *Details of the Liverpool CTC database have not been fully disclosed and cannot be properly assessed*. While the Liverpool CTC database is fundamental to the conclusions reached in the ACD, Boston Scientific is unable appropriately to understand the database and the way in which information has been collected, based on the material available in order to comment effectively on its use in this appraisal. We have reviewed the published data relating to the database[ii] as well as the explanations provided in the Assessment Report, however, it remains unclear how the data included in the Liverpool CTC database have been collected, how the data have been affected by changing treatment practice over time and whether such changes have resulted in a biased patient sample. In our response to the Assessment Report we expressed concern that the identification of risk factors based on the database was inconsistent with the extensive experience and published scientific literature, in that it cast doubt on the validity of longer lesions, small vessels and diabetes as risk factors for repeat revascularisation. While the Appraisal Committee has accepted the importance of these risk factors (and indeed, they appear now to be accepted by the Assessment	Comments noted. The Appraisal Committee was aware of the views expressed by consultee and commentators about the CTC database. Therefore it did not accept all the parameters and assumptions in LRiGs model see FAD sections 4.3.4, 4.3.5, 4.3.6, 4.3.7, 4.3.10, 4.3.11, 4.3.12, 4.3.13 and 4.3.14. The Appraisal Committee considered BCIS's assumptions see FAD sections 4.2.23, 4.2.28, 4.3.13 and 4.3.14.

		Group), no consideration seems to have been given as to whether, in circumstances where the information drawn from the database with respect to the influence of risk factors is unreliable, this casts very substantial doubt on any use of the Liverpool CTC database for decision making purposes.	
Boston Scientific		**1.4 Failure to permit consultation in relation to Addenda to the Assessment Report contrary to NICE's procedures.** Following the initial Assessment Report, the Appraisal Committee requested further analyses from LRiG. The results of these analyses were presented in addenda to the Assessment Report and some (addenda 1-4) were subject to consultation. However, addenda 5 and 6 were issued, discussed and adopted during the Appraisal Committee meeting on 4th of July 2007 and used as the basis for the conclusions set out in the ACD, without being circulated for consultation, in breach of NICE's procedures. NICE's Guide to the Technology Appraisal Process states, paragraph 4.4.1.8 "*Consultees and commentators have 20 working days to submit their comments on the [Assessment] Report to the Institute. These comments are presented to both the Assessment Group and the Appraisal Committee as part of the Evaluation Report*". The Institute's 'Guide for Manufacturers and Sponsors' provides, page 17. "*You will be sent a copy of the Assessment Report and given the chance to comment on it…. Any comments you make on this report will feed into the first Appraisal Committee meeting as part of the Evaluation Report."* The failure to allow consultation on addenda 5 and 6 to the Assessment Report introduces a serious procedural flaw to this appraisal. The fact that consultees are allowed to comment on the work of the Assessment Group, before this is	Comments noted. For the consultation on the Addenda due process was followed, as described in sections 4.5.1.2 and 4.5.2.6 of the Guide to the technology appraisal process.

		considered by the Appraisal Committee is an important element of a fair process in circumstances where manufacturers have not been invited to attend the meetings of the Committee and submission made before the Committee has formed its initial view are more likely to be influential. **We therefore ask the Committee to reassess the cost-effectiveness of DES using its reference case methodology and the meta-analysis of RCTs performed for the clinical effectiveness section of the ACD**	
Boston Scientific		**2. <u>The selective approach used in the cost-effectiveness analysis</u>** Since the publication of the AG report in December 2005, Boston Scientific has consistently highlighted the flaws in the AG methodology, mainly: - the outlier CTC baseline revascularization rate for BMS, - the methodology of estimating effectiveness, and under-estimation of DES risk reduction - the definition of risk factors. Some of these comments were accepted by the Appraisal Committee, who specifically asked the AG to use the Scottish Registry and BASKET as more representative sources for repeat revascularization rates (Addendum 3 – page 47). However the AG failed to do so. The final parameters agreed by the Committee are detailed on page 31 and summarised in the following table	DESs are recommended in circumstances outlined in section 1.1. The Appraisal Committee was aware of the views expressed by consultees and commentators about the CTC database. Therefore it did not accept all the parameters and assumptions in LRiGs model see FAD sections 4.3.4, 4.3.5, 4.3.6, 4.3.7, 4.3.10, 4.3.11, 4.3.12, 4.3.13 and 4.3.14. The Appraisal Committee considered BCIS's

See	Parameter	Figure	Source
2.1	BMS absolute risk of	11%	BASKET? + Scottish

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<tr><td></td><td>revascularization general population</td><td></td><td>Registry?</td></tr>
<tr><td>2.2</td><td>BMS absolute risk of revascularization Small vessels</td><td>19%</td><td>BASKET corrected by risk factors from CTC database</td></tr>
<tr><td>2.2</td><td>BMS absolute risk of revascularization Long lesions</td><td>11.7%</td><td>BASKET corrected by risk factors from CTC database</td></tr>
<tr><td></td><td>Mean number of stents</td><td>1.571</td><td>CTC database</td></tr>
<tr><td>2.3</td><td>DES relative risk reduction</td><td>55%</td><td>Expert opinion based on BCIS literature review</td></tr>
<tr><td>2.3</td><td>DES relative risk reduction subgroups</td><td>n/a</td><td>n/a</td></tr>
<tr><td>2.4</td><td>Price premium</td><td>£600</td><td>2004/05 NHS PASA survey</td></tr>
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We explain below our continuing concerns in relation to the assumptions adopted by the Appraisal Committee for the purposes of the ACD:
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<td>assumptions see FAD sections 4.2.23, 4.2.28, 4.3.13 and 4.3.14.</td>
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<td>Boston Scientific</td>
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Absolute risk of revascularisation for BMS in the general population

The absolute rate of revascularisation used by the AG in its initial report was 7.43%, a rate accepted by the Appraisal Committee to be a clear underestimation of the reintervention rate of BMS (paragraph 4.3.6 ACD). (The low rate of revascularisation seen in the Liverpool CTC database reflects the flaws inherent in the database, described in detail in our previous letters (12 January 2006 and 25 April 2006).)

In 2006 the Committee had requested additional analysis (Addendum 3) and the
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<td>DESs are recommended in circumstances outlined in section 1.1.

The Appraisal Committee was aware of the views expressed by consultees and commentators about the CTC database. Therefore it did not accept</td>
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		project specification summary table clearly states that the CTC data is not representative of repeat revascularisation rates in patients and requests that the Assessment Group use data instead from the BASKET trial and the Scottish Registry. The AG failed to do so; no explanation for this failure is provided and we believe it has prejudiced the consideration of this appraisal by the Appraisal Committee, because the Committee was not provided with all information it required for review of the technologies under consideration. At the last Committee meeting an 11% revasularisation rate was adopted by the Committee. It is unclear how the Committee reached that figure. Although it is a more accurate figure compared to the initial underestimation, the BMS revascularisation rate **cannot be accurately described by the BASKET study**. - BASKET is a randomized controlled trial but remains a single-centre study conducted in a non-UK population, so may not be representative of current clinical or cost experience in the NHS - Furthermore the authors comment that patients refused to consent to participate in the study in cases where the referring physician had expressed a preference for DES, which may suggest that trial participants were perceived to be at lower risk of revascularisation and the fact that the revascularisation rates reported are lower than those elsewhere is likely to be attributable, at least in part, to recruitment bias. - BASKET primary endpoint was cost-effectiveness after 6 months. It is a very short follow-up. A secondary evaluation was planned at 18 months but there is no longer-term follow-up planned to confirm long-term effectiveness of DES vs BMS - The ACD only mentions BASKET but not the exact reference of the	all the parameters and assumptions in LRiGs model see FAD sections 4.3.6, 4.3.12, 4.3.13 and 4.3.14. The Appraisal Committee considered BCIS's assumptions see FAD sections 4.2.23, 4.2.28, 4.3.13 and 4.3.14.

		publication reporting the 11% revascularization rate for BMS. Our research found the 18-month follow-up reported in the European Heart Journal in 2007[iii]. Results at 12 months, especially revascularization rates, are not clearly reported but can only be read from a graph. This is not a proper basis for calculating the reintervention rate for BMS. Alternatively, if the AG has had direct access to the BASKET investigators, this should be stated and the data and information provided shared with consultees. - Finally, the definition of TVR has been changed and was reported as non-MI related TVR at 18 months. This underestimates the number of revascularisations reported as TVR because at 6 months this was reported as 'all' TVR. Reference is also made to a figure of 11.5% from the Scottish registry. The Committee asked that the Assessment Group use the figure from the Scottish registry and NICE received the following from NHS QIS (13 January 2006): *"The Scottish Coronary Revascularisation Register Report for 2003-04 reports a repeat revascularisation rate at 12 months of 12.9% (95%CI 12.1-13.7; n=6525 vs 7.79% in Liverpool) for patients undergoing elective PCI and 16.6% (15.7-17.6; n=5921 vs 10.15% in Liverpool) for patients undergoing PCI for unstable coronary syndromes."* Combining these data in the correct proportions of acute coronary syndrome (ACS) and non-ACS patients (44% ACS, Ludman 2006), the absolute risk of repeat revascularisation for the unselected population is 14.5%. In the original appraisal of DES (2003) the Assessment Group used a BMS revascularization rate of 12.7%. There is no explanation as to why this rate may	

		have significantly changed in the intervening period up to this ACD. It seems that the Committee was willing to rely on data from BASKET and the Scottish registry because it did not have any angiographic outcomes and therefore did not report any protocol-driven revascularisations. However, the results from the preponderance of the available RCTs are also supported by the "real world" data from patient registries.	

Absolute risk of repeat revascularisation for BMS (no protocol mandated angiogram): published evidence

Source	Population (N)	No. of revascs (n)	% Revascs	Follow-up	Weight
Bagust et al, 2005	2,884	255	8.8%	12m TVR, CTC clinical database	5.3%
Shrive et al, 2005	7,334	601	8.2%	12m any revasc, clinical database	13.4%
Singh et al, 2005	11,484	1,609	14.0%	PRESTO trial. 9m TVR, ischaemia-related revasc	21.0%
Jilaihawi et al, 2005	1,003	51	5.1%	12m TLR, clinical database	1.8%
Serruys et al, 1998	206	16	7.8%	BENESTENT II trial.12m TLR no angio group	0.4%
Gershlick et al, 2004	38	6	15.8%	ELUTES trial control group.12m TLR symptom driven revasc	0.1%
Stone et al, 2004	385	49	12.7%	TAXUS IV trial control group.12m TLR no angio cohort	0.7%
Homes et al, 2004	525	85	16.2%	SIRIUS trial control group.12m TLR angina driven revasc	1.0%
Lemos et al, 2004	380	41	10.8%	12m TVR angina driven, clinical database	0.7%
Serruys et al, 2001	600	102	17.0%	ARTS trial stent arm.12m all revascs, no follow-up angio	1.1%
Wu et al, 2004	3,571	577	16.2%	12m revasc, prospective registry of routine practice	6.5%
Agema et al, 2004	3,177	304	9.6%	9m TVR in routine clinical practice	5.8%
Gotschall et al, 2006	848	63	7.4%	12m TVR, clinical database	1.6%
Ellis et al, 2004	5,239	702	13.4%	9m all revascularisations, clinical database	9.6%
Brophy et al, 2005	16,746	2143	12.8%	9m re-intervention, clinical database	30.6%
Kaiser et al, 2005	281	22	7.8%	6m TVR, BASKET trial, no angiogram	0.5%
Overall	**54,701**	**6,626**	**12.1%**		**100.0%**

- Studies in red were cited in the Assessment report. The 2 largest studies (Singh et al and Brophy et al) were not cited.
- Liverpool database constitutes 5% of the patients in the literature.

The above chart is taken from public domain evidence (BCIS and BCS response to AR Supplement 3 and 4) and demonstrates that 'real world' registry outcomes for the absolute risk of revascularization reflect the results from the major RCTs.

Boston Scientific		**Absolute risk of revascularization for BMS for high-risk subgroups: patients with small vessels and long lesions** In the original TAR the AG discounted vessel size and lesion length as independent risk factors, based on data from the Liverpool CTC database, in contradiction to the original NICE Appraisal from 2003. The Committee consequently requested the AG to assess the relative risks of the independent risk factors (small vessel, long lesion and diabetes) taken from the major RCTs. In Addendum 3 to the Assessment Report, the AG analysis recognised these as significant factors and this was also the conclusion of the Appraisal Committee, casting doubt on the credibility of the CTC database as a whole. However, despite recognising the unreliability of the Liverpool CTC database in terms of the identification of risk factors, the Appraisal Committee based the rates of revascularisation for small vessels and long lesions for the purposes of the ACD, on the risk factors used by the Assessment Group and taken from the CTC – 19% for small vessels and 11.7% for long lesions. No explanation for the reliance on these figures has been provided. Furthermore, we believe that the selective use of data demonstrated by this approach is unbalanced and unscientific. Completely different sources of evidence have been considered and arbitrarily bolted together, apparently without consideration as to whether this is a valid strategy, when the relative risk for subgroups drawn from the CTC database are applied to the 11% non-MI related TVR from BASKET. **A consistent approach should be taken by the Committee. Data from DES**	The Appraisal Committee was aware of the views expressed by consultees and commentators about the CTC database. Therefore it did not accept all the parameters and assumptions in LRiGs model see FAD sections 4.3.4, 4.3.12, 4.3.13 and 4.3.14 of the FAD. The Appraisal Committee considered BCIS's assumptions see FAD sections 4.2.23, 4.2.28, 4.3.13 and 4.3.14.

		RCTs provide clear and consistent clinical outcomes for several subgroups including patients with small vessels and long lesions. In circumstances where the Committee has recognised the unreliability of the Liverpool CTC database for the consideration of risk factors, it is illogical to use these data for the purposes of the assessment.	
Boston Scientific		**<u>Relative risk reduction with DES</u>** When considering relative risk reduction with DES, the Committee relied on the clinical specialists quoting rates from RCTs in the range of 50-60% for the base case (general population) and 60-70% for high-risk groups. The Committee adopted a 55% rate for the base case and 65% in the sensitivity analysis. - We agree with the decision from the Committee to rely on RCTs to assess efficacy of DES, however the results should be based on a comprehensive systematic review of the available literature. The meta-analysis performed by the AG for the clinical effectiveness section should be used to inform DES effectiveness in the base-case of the economic analysis. - We would also urge the Committee to draw from the meta-analysis of RCTs a ***distinct risk reduction for each high-risk subgroup*** (small vessels, long lesions and diabetics). There is overwhelming evidence in the literature that DES are particularly effective in certain high-risk subgroups. Applying the same risk reduction to the general population and the subgroups greatly underestimates the benefits provided by DES.	The Appraisal Committee did not accept all the parameters and assumptions in LRiGs model see FAD sections 4.3.4, 4.3.7, 4.3.12, 4.3.13 and 4.3.14. The Appraisal Committee considered BCIS's assumptions see FAD sections 4.2.23, 4.2.28, 4.3.13 and 4.3.14.

		- The above statement can be illustrated by the initial NICE Technology Appraisal from 2003 that identified small vessels and long lesions as two subgroups where the additional clinical benefits made DES cost-effective. - It can also be illustrated by the BASKET cost-effectiveness analysis. This study did find that DES were cost-effective in elderly patients and specific high-risk subgroups. In a press conference at the ESC Congress in 2005, Dr Pfisterer from the BASKET investigators estimated that the proportion of patients that might fall into the category of high risk, such that a DES would prove cost-effective, would be around two thirds to three quarters of all patients.[iv] This estimate tallies with current DES use in the NHS which is around 60%. **The Committee should rely on the meta-analysis from all RCTs with subgroup data to derive a distinct risk reduction for all subgroups.**	
Boston Scientific		**Price premium** The price difference between BMS and DES is a critical aspect of the model and the ICER is highly sensitive to the price premium. The ACD quotes a general price premium of £600.00. This figure was derived from a NHS PaSA survey conducted in 2004/05 which covered 20 NHS Trusts. We believe that this figure should not be relied upon for the purposes of the appraisal: The survey itself is uninterpretable as there was no clear explanation of methodology used, the centres selected or what proportion of the market they represented at the time. Furthermore, since the survey was conducted, the market has changed	Comments noted. The Institute has received data from PASA for 2007/08 see FAD section 3.6.

		dramatically - In 2004/05, prices of BMS had already reduced drastically as DES quickly penetrated the market and reduced the prices of the older technology which predated it; - DES are now used on a routine basis in the NHS, in around 60% of PCI cases; - There have been new entrants to the DES market thus bringing about price reductions from when the first DES was launched in the UK. Suppliers work in a highly competitive environment where every point of market share is keenly contested. This has led to rapid reductions in purchase prices where the market operates effectively to the benefit of the NHS buyer and the taxpayer. There is no immediate way that the Institute can reference prices nationally as this remains a dynamic market characterized by rapid evolution and development but the assumptions made in the ACD are not at all reflective of current market conditions. By the time this Guidance is published these assumptions will be 4 years old and will be of no value to anyone responsible for planning NHS budgets and services. It should also be stated that the reduction in purchase price of BMS is in part a result of a market existing for DES. If that market is taken away then there is no guarantee that current BMS pricing models will be maintained. The ACD on page 32 states that there is no national procurement of DESs as a price premium that would fall below £300. We would comment that the ACD is not the place to be attempting to influence procurement policy in the NHS as this would exceed the Institute's powers.	

		We would like to point out to the Committee that the best source of evidence might be the latest tender from the HPC/LPP procurement hubs as they cover approximately 20% of the English market.	
Boston Scientific		**3. <u>Bias from the Assessment Group</u>** The Assessment Group has an important conflict of interest in the context of this appraisal and we believe this has prevented a proper impartial review of the evidence as required for a fair assessment. The approach followed by the Assessment Group in assessing DES is novel and highly controversial. This is based on a paper by members of the Assessment Group (Bagust *et al)*, this has been comprehensively challenged by Dr Martyn Thomas[v], and by the BCIA at the time of publication and these responses are well-documented. However, the methods and conclusions of the Bagust *et al*. paper are reflected in the Assessment Report. The public views of the Assessment Group and their interest in supporting their own research conclusions creates a substantial conflict with the requirement to carry out an impartial review for the purposes of the NICE appraisal. The importance of these types of interest is properly reflected in the requirements of the Institute's Code of Practice on declarations of interest which provides that the following non-pecuniary interests should be declared by members of NICE's Board, its advisory committees and experts invited to attend meetings of the Appraisal Committee: 3.5 **A personal non-pecuniary interest** in a topic under consideration might	Comment noted. The Assessment Group began working on this appraisal in 2005 therefore the Code of Practice for Declaring and Dealing with Conflicts of Interest does not apply to this appraisal. Previously the Institute has assessed the situation and concluded that there was no conflict of interest.

		include, but is not limited to: i) a clear opinion, reached as the conclusion of a research project, about the clinical and/or cost effectiveness of an intervention under review ii) a public statement in which an individual covered by this Code has expressed a clear opinion about the matter under consideration, which could reasonably be interpreted as prejudicial to an objective interpretation of the evidence In this case, however, the Assessment Group has made no declaration in respect of this clear conflict of interest either in the Assessment Report itself or at any of the meetings of the Appraisal Committee attended by members of the Assessment Group. This represents a clear breach of NICE's procedures and prevented the Appraisal Committee being placed in a position where it could take into account such conflict of interest when weighing the conclusions expressed in the Assessment Report. The effect of this failure properly to address the conflict of interest is substantial. The Assessment Report is a central part of the evidence considered by the Appraisal Committee and, in this case, the Committee has accepted the controversial approach followed by the Assessment Group, without any recognition of the difficulties created by the Assessment Group's previous work. In view of the very serious issues we have raised in relation to this approach, we believe it is essential that the Appraisal Committee seeks an independent review of the evidence from an impartial group and following consultation on their assessment, prepares a fresh ACD.	
Boston Scientific		**4. <u>Overall impact on the NHS and on patient care</u>** The original guidance established by NICE in September 2003 proved to be a major contributor to the achievement of the NSF targets on revascularisation	DESs are recommended in circumstances outlined

		and was viewed in many other countries as the benchmark for clinical guidance in this area. The European Society of Cardiology guidelines are very much in line with this guidance and it would be a volte face on a grand scale were the current draft guidelines to be adopted. In this section there will be an examination of the likely impacts of an attempt to implement this draft guidance: **i. Patient care and Patient Choice** In section 2.5 of the ACD it states that the outcome of CABG vs stenting is not covered by this review. However, were these guidelines to be adopted, there will be an upsurge in the number of CABG referalls within the NHS. Even if we take one of the main planks of this review, BASKET, and use the findings within that trial, we could expect to see an additional 22% CABG cases as a result of the removal of DES from the market - "*Neither did we assess cost savings due to reduced rates of bypass surgery (-22% during the BASKET experience at the University Hospital of Basel)*."[vi] (p928) The results of treatment with DES are well known. Worldwide millions of patients have been treated with DES and in the UK there are over 100,000 patients who have benefited from this treatment and technology. The technology has been covered on a number of occasions in the popular media. In section 2.3 of the ACD it is stated that incidence of CAD is higher amongst the lower socio-economic groups. Therefore we can assume that the backward step suggested by the preliminary findings contained in the ACD will disproportionally effect people in lower socio-economic groups whilst, given general public awareness of the availability of this technology (and, by the admission in the ACD, of its superior outcomes), that we are likely to see an upsurge in the private market for those in higher socio-economic groups who are either insured or willing to pay for this treatment, whilst where there is greater prevalence but less ability to pay, a large number of those patients will be condemned to painful and expensive surgery. Notwithstanding the inequity of this situation there is also an	in FAD section 1.1.

		economic impact of this restriction of therapy choice which will be examined in the following section. **ii. Commissioners** As stated above the 'choice' being presented in this ACD is not a straight swap between the use of a DES or a BMS. Around 40% of patients are currently treated with a BMS in PCI procedures now as a result of clinicians making informed effectiveness decisions on a daily basis within the NHS. As suggested by BASKET there could be an increase in the region of 22% in CABG referrals if DES are no longer available in the NHS market. Therefore of the current ~ 70,000 PCI procedures annually we could expect to see around 9,000 new CABG cases per annum (22% of the 60% of cases where DES are used). The elective tariff for 2007/8 for CABG is set at £7,375. Thus we can anticipate additional costs to PCTs of over £56M per annum. The elective tariff for PCI is set at £3,752 therefore each of these patients will cost the PCT an additional £3,623. In addition to this commissioners will have to find an additional 36,000 acute bed days (assuming CABG length of stay = 5, PCI = 1) from a system that is already 'running hot'. This is likely to jeopardise attempts to achieve waiting time targets coming from a baseline where cardiac waiting lists have largely been eliminated. **iii. Providers** The large investment in PCI infrastructure over the last 8 years will be called into question and the scramble to free up acute beds will begin. On a daily basis clinicians and managers will be assailed by patients who are aware of the superior technology but also know that it is being denied to them. Clinician behaviour over the last 4 years (selective deployments of a new technology, increasing familiarity and rapid adoption followed by therapy maturity and a	

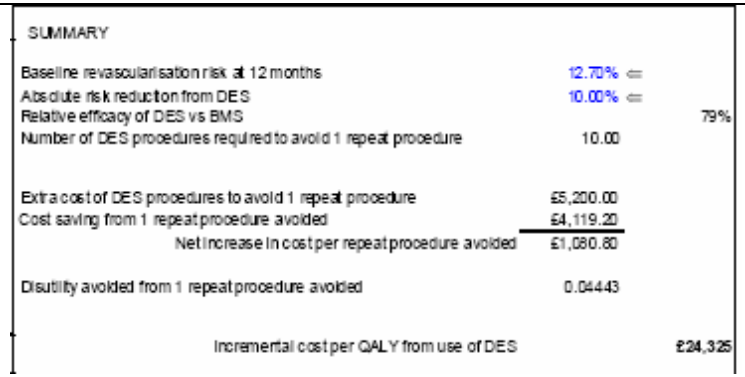
		'settling' at around 60% of cases) demonstrates that they will still believe in the patient benefits of DES and will want to use them but will be dissatisfied and de-motivated by this denial. Some very difficult decisions will have to be made, on a regular basis, regarding 'surgical turn-downs'.	
Boston Scientific		***Conclusion*** To a reasonably well-informed observer, the preliminary ACD has seemingly been based on a controversial and criticised approach to assessment, disregarding the huge body of evidence surrounding DES. In circumstances where the Assessment Group has an undeclared conflict of interest, this creates an impression of lack of impartiality and unfairness. As a consequence, the assessment of cost effectiveness is flawed and the NHS becomes the only healthcare system in the developed world that denies patients this treatment option (despite being fuelled by the 5th largest economy in the world). In view of the established benefits associated with DES treatment, a private market develops where DES *are* used, thus increasing the health inequalities that as a society we have been trying to reduce over the last 10 years as a matter of policy. At the same time costs per NHS patient actually rise in over 20% of cases and there are not enough beds to absorb this newly-required capacity which has a knock-on effect to many other in-patient services and further squeezes cash in the system. Some of the few high-profile, undeniable gains following years of investment in the NHS, increased revascularization rates and the elimination of waiting times, are sacrificed for the sake of £600.00 per patient – an inaccurate and inflated figure taken from an unrepresentative sample from 4 years ago.	Comments noted. DESs are recommended in circumstances outlined in FAD section 1.1. The Committee did not accept all the parameters and assumptions in LRiGs model see FAD sections 4.3.4, 4.3.5, 4.3.6, 4.3.7, 4.3.10, 4.3.11, 4.3.12, 4.3.13 and 4.3.14.
Boston	4.1.10	*For TLR, the meta-analyses showed statistically significant differences in favour*	Comment noted.

Scientific		*of any-type DES over any-type BMS, with improved rates of lesion revascularisation at all follow-up time points up to 3 years. (page 12)* This conclusion was drawn from an analysis of 17 RCTs reinforcing the clinical benefit of DES technology	
Boston Scientific	4.1.7	As the time frame being considered for cost effectiveness is 12 months we request that the statement in 4.1.21 (page 16) is removed: "*A statistically significant reduction in TVR with the SES (Cypher) compared with the PES (Taxus) was determined from a meta-analysis of two trials at 6-9 months (OR 0.59, 95% CI 0.39 to 0.89). A reduction in the composite event rate (MACE) at 6-9 months was also statistically significant with the SES (Cypher) compared with the PES (Taxus) (OR 0.75, 95% CI 0.59 to 0.96)*."	Comment noted. FAD Section 4.1 summarises the clinical effectiveness evidence that was available when the assessment report was produced and therefore available to the Appraisal Committee.
Boston Scientific	4.1.25	*The pooled DES analysis indicated that revascularisation rates were reduced by approximately three quarters compared with BMSs, consistent across most studies of the PES (Taxus) and the SES (Cypher [Endeavor at 6–9 months]). The benefits of DESs over BMSs for TLR were seen at 1 year, and this significant difference was maintained up to 3 years. For the outcome TVR there were statistically significant differences in favour of any-type DES over BMS for most of the time points assessed.* This conclusion demonstrates the consistency of benefit derived from the use of DES. It does not tally with the AGs decision to use BASKET at the single source of inputs for absolute benefit of DES.	The Appraisal Committee did not accept all the parameters and assumptions in LRiGs model see FAD sections 4.3.6 and 4.3.7.
Boston Scientific	4.2.20	*The Assessment Group also undertook new sensitivity analyses that took account of an additional 9 months use of clopidogrel in patients receiving DESs* The IFU for Taxus advises use of clopidigrel for 6 months. Calculations for	The Appraisal Committees considerations of this point is described in FAD sections 4.1.22 and

		additional costs for the use of this stent should be based on 6 months, not 9 months.	4.3.10.
British Cardiovascular Industry Association		**Introduction** BCIA strongly disagree with the draft guidance set out on the ACD. There are profound implications to withdrawing from the NHS, DES technology that has been in use for five years. Our responses to the ACD are set out under four categories: • Has all the relevant evidence been taken into account? • Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence and are the preliminary views on the resource impact and implications for the NHS appropriate? • Are the provisional recommendations sound and do they constitute a suitable basis for the preparation of guidance to the NHS? • Are there any equality-related issues that may need special consideration?	Comments noted.
British Cardiovascular Industry Association		**Has all the relevant evidence been taken into account?** The numerous submissions in the Evaluation Report show that consultees have repeatedly demonstrated that LRiG have consistently failed to present all the available evidence pertaining to: ▪ The DES price premium ▪ The absolute risk of repeat revascularisation with BMS ▪ The risk reduction associated with DES ▪ The risk factors for repeat revascularisation	Comments noted.
British Cardiovascular		**DES Price Premium** BCIA will not engage in discussion of prices due to issues around anit-trust and	Comments noted. The Institute has received data

Industry Association		competition law. We simply request, for transparency and methodological reasons, clarification of how the DES price premium identified in section 4.3.11 of the ACD was determined. What sources were used – list prices or market prices? What time point do the sources refer to? The reference to national procurement of DES in section 4.3.13 of the ACD is ill-advised, as the Institute would be exceeding its powers if such a statement were perceived to be making recommendations on procurement policy. The Institute needs to find ways of dealing with a number of issues unique to devices that it does not often face with pharmaceuticals. Pharmaceutical prices tend to be reasonably constant over time whilst they have patent protection and decrease only when generic competition enters the market. Devices, on the other hand, do not benefit from long periods of market exclusivity and lifecycles are relatively short compared with drugs, in turn resulting in greater market price competition. Prices therefore fall more quickly than with drugs and this Review over-simplifies the market conditions for stents. A wider understanding of the market conditions is required. BMS prices have fallen at the same time as, and probably as a result of, falling DES prices. The Institute's methods must take account of these dynamics because the ICER as a sole decision-making tool becomes unreliable in this situation, particularly given the fact that the ACD states that the effectiveness of DES has not diminished. If device price dynamics were not taken into account, there would potentially be regression to the least expensive therapy even if it had already been rendered clinically obsolete in many patients.	from PASA for 2007/08; see FAD sections 3.5 and 3.6.
British Cardiovascular Industry		**The Absolute Risk of Repeat Revascularisation with BMS** The ACD states that the absolute risk of repeat revascularisation with BMS have been chosen to be 11% for all patients, based on 10% for elective patients and	The Appraisal Committee did not accept all the parameters and

Association		13% for non-elective patients. It is not clear how these rates have been determined, because submission to NICE by NHS QIS (dated 13th January 2006) states: *"The Scottish Coronary Revascularisation Register Report for 2003-04 reports a repeat revascularisation rate at 12 months of 12.9% (95%CI 12.1-13.7; n=6525 vs 7.79% in Liverpool) for patients undergoing elective PCI and 16.6% (15.7-17.6; n=5921 vs 10.15% in Liverpool) for patients undergoing PCI for unstable coronary syndromes."* As the Appraisal Committee requested that the Scottish registry be used to inform the base case scenario in the economic model (specification of additional work, February 2006), we would have expected this to be implemented. Combining these data in the correct proportions of acute coronary syndrome (ACS) and non-ACS patients (44% ACS, Ludman 2006), the absolute risk of repeat revascularisation for the unselected population is **14.5%**. This is clearly a case where relevant evidence was identified by the Appraisal Committee, but is has not been taken into account in the economic model. It is perverse to specify use of a data input and then later ignore it. It is also of note that the 2003 Appraisal employed a BMS revascularisation rate of 12.7% (LRiG 2003 Addendum B, page 35), but this evidence appears to have been omitted from deliberations. As there is no evidence that BMS repeat revascularisation rates have fallen since 2003, how can a reduction in the base case rate in the model be justified in this review? A copy of the relevant section of the 2003 model is reproduced in Figure 1:	assumptions in LRiGs model see FAD sections 4.3.6, 4.3.12, 4.3.13 and 4.3.14 of the FAD. The Appraisal Committee considered BCIS's assumptions see FAD sections 4.2.23, 4.2.28, 4.3.13 and 4.3.14.

		 SUMMARY Baseline revascularisation risk at 12 months 12.70% ⇐ Absolute risk reduction from DES 10.00% ⇐ Relative efficacy of DES vs BMS 79% Number of DES procedures required to avoid 1 repeat procedure 10.00 Extra cost of DES procedures to avoid 1 repeat procedure £5,200.00 Cost saving from 1 repeat procedure avoided £4,119.20 Net increase in cost per repeat procedure avoided £1,080.80 Disutility avoided from 1 repeat procedure avoided 0.04443 Incremental cost per QALY from use of DES £24,325 **Figure 1. Baseline risk and absolute risk reduction used in the 2003 Appraisal of DES.**	
British Cardiovascular Industry Association		**The Risk Reduction Associated with DES** We welcome the fact that the Appraisal Committee have recognised that a 41% reduction in repeat revascularisation risk under-estimates the effectiveness of DES, but the use of 55% risk reduction is still flawed. The model should be re-run using the treatment effects taken from the randomised trials evidence for both MI and TLR submitted in Section 2 of this response. This would be consistent with the Institute's Methods Guide, which states that all relevant evidence should be used and randomised trials are ranked first in the hierarchy of evidence for measures of relative treatment effect. Given that the Appraisal Committee have recognised that the clinical benefit of DES is sustained, it is unclear why the current economic model employs a risk reduction of 55% when the model used in the 2003 Appraisal used 79%.	The Appraisal Committee did not accept all the parameters and assumptions in LRiGs model see FAD sections 4.3.4, 4.3.7, 4.3.12, 4.3.13 and 4.3.14. The Appraisal Committee considered BCIS's assumptions see FAD sections 4.2.23, 4.2.28, 4.3.13 and 4.3.14.

British Cardiovascular Industry Association		**Risk Factors for Repeat Revascularisation** We recognise that the Appraisal Committee have accepted long lesions and small vessels as risk factors for repeat revascularisation. With respect to diabetes as an independent predictor of repeat revascularisation, the ACD suggests in section 4.3.4 that there is still some doubt over diabetes as a risk factor. Consultees' responses to the Assessment Report Addendum presented seven studies not cited by LRiG, five of which identified diabetes as an independent predictor, along with two others previously identified. Of the 14 literature sources identified, diabetes was the second most commonly occurring independent risk factor (in 7 out of 14 datasets). It is remarkable that this evidence from the entire literature has not prompted a clear statement that diabetes is an independent predictor of repeat revascularisation. In the latest cost effectiveness analysis (Addendum 6') LRiG have used an unusually low relative risk (RR) for diabetes (1.19). This results from the sole reliance on the CTC database and a combination of relative risks of 0.90 for non-elective patients and 1.38 for elective patients (Addendum 4'). It is notable that the British Cardiovascular Intervention Society (BCIS) have adopted a more reasonable approach in their response to Addenda 3'' and 4', in deriving relative risks from the wider literature. BCIS identify a RR of 1.52 for diabetes (range 1.34 to 1.81) and LRiG should have noticed that in comparison, the CTC dataset has produced an apparently spurious result that is driven by the peculiar RR of 0.90 for non-elective patients. It is most odd to quote a RR of <1 for a risk factor that has been shown to increase the relative risk and is perverse in the light of the other evidence submitted. This is a clear example of LRiG failing to take all the relevant evidence into account and it would be more reliable to run the economic used to produce Addendum 6' (that informed the ACD) using the BCIS mean relative risk of 1.52. LRiG's relative risks for the individual risk	With regard to diabetes as a risk factor see FAD sections 4.1.23, 4.1.24 and 4.3.4. The Appraisal Committee considered BCIS's assumptions see FAD sections 4.2.23, 4.2.28, 4.3.13 and 4.3.14.

		factors of small vessels and long lesions are within the ranges in the wider literature and on that basis, although somewhat low for long lesions, seem reasonable.	
British Cardiovascular Industry Association		**Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence and are the preliminary views on the resource impact and implications for the NHS appropriate?** The summaries of clinical and cost effectiveness are not reasonable on the following grounds: The source of the DES price information is unclear. Judgements on interpretation of the resource impact for the NHS cannot be made unless there is transparency over the source of such a critical factor. The absolute risk of repeat revascularisation has been unreasonably reduced compared with the rates submitted from the Scottish registry and those used in the original DES appraisal. The risk reduction associated with DES has been unreasonably reduced compared with the rates from the randomised trials. This deviates from the Institute's Guide to the Methods of Technology Appraisal (section 3.2.2.1), which states ***".....RCTs are therefore ranked first in the hierarchy of evidence for measures of relative treatment effect."*** Removal of DES from the NHS will have an undoubted effect on NHS service provision in that some patients who may currently be treated by PCI with DES will in future need to be referred to CABG because the restenosis risk with BMS will simply be too great. The potential impact can be estimated as follows: The 58,576 PCIs in England and Wales in 2005 (Ludman 2006) models to	Comments noted. DESs are recommended in circumstances outlined in FAD section 1.1. The Appraisal Committee did not accept all the parameters and assumptions in LRiGs model see FAD sections 4.3.4, 4.3.5, 4.3.6, 4.3.7, 4.3.10, 4.3.11, 4.3.12, 4.3.13 and 4.3.14. The Appraisal Committee considered BCIS's assumptions see FAD sections 4.2.23, 4.2.28, 4.3.13 and 4.3.14.

		67,809 PCIs in 2008, assuming a conservative growth of 5% per year. If 20% of these patients are referred back to CABG, surgery has to increase capacity by 13,562 procedures from a standing start in 2008. Bearing in mind that there were 22,724 CABG procedures in 2005 and CABG has not shown growth, this equates to a potential demand for a 40% increase in CABG. It is highly unlikely that surgery will be able to accommodate this extra demand and waiting times will inevitably increase. This, at a time when the 18 weeks waiting time policy has to be implemented. Government will not meet its targets. In addition, the CABG reference cost, at a weighted average of £8,198, is 2.54 times than PCI with DES at £3,231. This cost differential means that the NHS will have to pay an extra £67.4 million to achieve the same number of revascularisation procedures. In addition, the NHS will also have to fund an additional 4,231 repeat revascularisation procedures (based on the current LRiG model) at a cost of £16.2 million. Thus, the gross cost would be approximately £83.5 million. Assuming current DES usage of 60% and an incremental cost of £870 per DES procedure (LRiG model), the cost avoided by this draft guidance becoming final would be £28.3 million. The net cost to the NHS is therefore likely to be £55.2 million in 2008 alone. The ACD does not take these costs and service implications into account and this estimate takes a conservative view of the potential shift back to surgery.	
British Cardiovascular Industry Association		**Are there any equality-related issues that may need special consideration** NHS Scotland allows DES to be used so this draft guidance would create cross-border inequalities within the UK. Patients who can afford private treatment are likely to pay for PCI with DES rather than risk restenosis with BMS in the NHS, or have CABG. This will create a two-tier health system whereby those who can afford DES will pay for them.	Comments noted. DESs are recommended in circumstances outlined in FAD section 1.1.

British Cardiovascular Industry Association		**<u>Potential Solutions</u>** The model should be re-run incorporating: The absolute risk of repeat revascularisation from the Scottish registry, now known to be 14.5% for an unselected population without protocol-mandated angiographic follow up. Long lesions, small vessels and diabetes as risk factors, but using a literature-based relative risk of 1.52 for diabetes. LRiG's relative risk of 0.90 for non-elective patients is clearly unrepresentative. Treatment effects based on the randomised trials as identified by BCIS in their response to Assessment Report Addenda 3'' and 4'. The Evaluation Report shows that consultees have repeatedly demonstrated LRiG's failure to present the Appraisal Committee with all the relevant evidence on many occasions. These failures may well be due to the LRiG's unwillingness to contradict their pre-formed opinion on the cost effectiveness of DES, published prior to the deadline for submissions by consultees. LRiG would be required to declare this publication under NICE's current conflict of interest policy, something they have yet to do. Given the clear and documented problems that this has created throughout, we call for this Review to be referred to the Decision Support Unit to ensure that all relevant and up-to-date information is taken into account.	Comments noted. The Appraisal Committee did not accept all the parameters and assumptions in LRiGs model see FAD sections 4.3.4, 4.3.5, 4.3.6, 4.3.7, 4.3.10, 4.3.11, 4.3.12, 4.3.13 and 4.3.14. The Appraisal Committee considered BCIS's assumptions see FAD sections 4.2.23, 4.2.28, 4.3.13 and 4.3.14. The Assessment Group began working on this appraisal in 2005 therefore the Code of Practice for Declaring and Dealing with Conflicts of Interest does not apply to this appraisal. Previously the Institute has assessed the situation and concluded that there was no conflict of interest.

British Cardiovascular Society and British Cardiovascular Intervention Society		This document constitutes the British Cardiovascular Society and British Cardiovascular Intervention Society official response to the above "Appraisal Consultation Document". Members and executives of these societies remain deeply concerned with the conclusions of the draft guidance and resolutely determined to highlight the inadequacies of the Liverpool Assessment Group and the means by which the conclusions were reached. We truly fear that should the Guidance be implemented this will be a major and fundamentally important retrograde step for British Cardiology. We will address the document under the headings suggested.	Comments noted.
British Cardiovascular Society and British Cardiovascular Intervention Society		**(i) <u>Do you consider that all the relevant evidence has been taken account?</u>** We had always been led to believe that appraisals developed by The National Institute for Clinical Excellence were fundamentally based on robust evidence and that their core analysis was driven appropriately by data from worldwide randomised trial literature. This has not been the case within this appraisal. We continue to be confused by the emphasis that has been placed on a single unsubstantiated audit and a single trial in the literature (the Basket Trial). The Liverpool CTC database was designed to assess the in-patient complications and local clinical outcomes of coronary angioplasty. Since it cannot be regarded as being robust in terms of known and confirmed outcomes, this local audit has in the setting of this appraisal, which depends on robust knowledge of absolute outcome data, been used inappropriately. We have previously explained to the Committee (on a number of occasions) that there was no systematic follow up of patients, that some patients developed	Comments noted. The Appraisal Committee was aware of the views expressed by consultees and commentators about the CTC database. Therefore it did not accept all the parameters and assumptions in LRiGs model see FAD sections 4.3.4, 4.3.5, 4.3.6, 4.3.7, 4.3.10, 4.3.11, 4.3.12, 4.3.13 and 4.3.14. The Appraisal Committee considered BCIS's

		symptoms but did not undergo a repeat revascularisation within a year (because of waiting list issues) and that patients who received a repeat revascularisation at another hospital did not appear on the database. Such factors, together with a systematic bias against high risk patients (demonstrated by the low diabetes rate in the cohort), result in an unrealistically low repeat revascularisation rate of 7.43%. Dr Rod Stables and other cardiologists at CTC confirm the inadequacy of the Liverpool database for a NICE type of appraisal. The committee also appears to acknowledge this because they eventually decide on a rate for repeat revascularisation in a general population in the final appraisal document of 11%. The risk factors for repeat revascularisation that "fell out" of the Liverpool Assessment Group analysis using the CTC database are unquestionably unique in the world literature. Multiple properly performed trials and registries have repeatedly shown small vessels, long lesions and diabetics to be the populations at high risk of needing a repeat procedure. This either means the Liverpool patients are unique or that there is a systematic bias in patient selection and treatment methods. Once more the committee appear to acknowledge this by dismissing the idea that there may be a difference between elective and non-elective patients, something that only the Liverpool Assessment Group analysis of the CTC database has found. The situation becomes confusing and compounded since subsequently data from the Liverpool database is used to calculate the relative risk of repeat revascularisation in patients with small vessels, long lesions and diabetes. Once more the committee appear to have agreed that these are high risk patients (merely by asking the Liverpool Assessment Group to carry out a subsequent analysis on the world recognised high risk groups). What should have happened then of course was for the committee to ask the Liverpool Assessment Group to undertake this high risk group analysis using the independently adjudicated, peer-reviewed and published, randomised controlled trial data. Even the much touted Basket trial agrees that these factors do increase subsequent revascularisation and that these are the very patients who benefit from the use	assumptions see FAD sections 4.2.23, 4.2.28, 4.3.13 and 4.3.14.

		of drug eluting stents (DES). To then use the Liverpool data for repeat revascularisation in these high risk groups rather than the world literature appears utterly perverse, inappropriate and illogical as we already know that due to the systematic bias of the registry these factors had not appeared to increase the risk of revascularisation. Therefore the data and the numbers that are generated must be suspect. At the beginning of this appraisal the British Cardiovascular Intervention Society contacted NICE to indicate that we felt that the Liverpool Assessment Group had a fundamental conflict of interest and were not the appropriate group to carry out the review. Given that this group had already published a negative manuscript on the cost effectiveness of DES using the flawed CTC data, it is difficult to see how they could ever carry out an independent review. We presume that under the new conflict of interest rules of NICE Liverpool would currently be excluded from any such similar appraisal. If the committee continue to use this data for the basis of their evaluation, rather than the randomised literature, we believe the appraisal remains deeply flawed and thus, in this context, is worthless. In addition we believe this use of inadequate data and overall poor methodology will do great harm to the credibility of the NICE process.	
British Cardiovascular Society and British Cardiovascular Intervention Society		**(ii) <u>Do you consider that the summaries of the clinical and cost effectiveness are reasonable interpretations of the evidence and that the preliminary views on the resource impact and implications for the NHS are appropriate?</u>** It has been acknowledged in the Appraisal that DES are indeed clinically effective in reducing repeat revascularisation following percutaneous coronary intervention and that this difference reaches levels of high statistical significance.	Comments noted. The Appraisal Committee was aware of the views expressed by consultees and commentators about the CTC database. Therefore it did not accept all the parameters and

		The cost effectiveness model is critically dependent on 4 key variables. We believe the the numbers used for these variables in the Liverpool Assessment Group model are incorrect due to use of the flawed baseline CTC data. The committee have changed these values during the course of the appraisal but the final values remain illogically derived and appear to represent compromise values rather than being based on evidential science. We do not believe this is the methodology under which such a National Appraisal by NICE should take place. ***(a)*** *The absolute risk of repeat revascularisation with <u>bare metal stents</u>* The value used by the committee for target lesion revascularisation is 11%. We are unclear how this was derived, but paragraph 4.3.6 of the Appraisal Consultation Document suggests that it is a "compromise figure"; in any event it has not been derived from published data or recognised scientific methodology. It would appear that the Committee appropriately disbelieve the Liverpool Assessment figures but cannot quite come to accept the figures from the randomised controlled trials and from the substantial and peer reviewed published registry data. We initially shared with the committee the data from such randomised trials and real world registries, both with and without angiographic follow up, indicating that the baseline bare metal stent repeat revascularisation rate is > 12%. We understand that some members of the committee felt that high repeat revascularisation rates were driven by trial protocol, particularly routine follow-up angiography. We have however provided to the committee similar figures for repeat revascularisation in the randomised trials that did not mandate angiographic follow up.	assumptions in LRiGs model see FAD sections 4.3.4, 4.3.5, 4.3.6, 4.3.7, 4.3.10, 4.3.11, 4.3.12, 4.3.13 and 4.3.14. The Appraisal Committee considered BCIS's assumptions see FAD sections 4.2.23, 4.2.28, 4.3.13 and 4.3.14.

		The Committee subsequently referred us to the Scottish Revascularisation Registry; this reports a repeat intervention rate, after implantation of a bare metal stent and without mandated angiography, of 13% and, in contrast to the Liverpool CTC data, has been both peer reviewed and published. We should emphasize that the Committee were drawn towards The Scottish Revascularisation Registry data as it is not based on mandated angiograms and reflects UK clinical practice in the ”real world”; it is therefore the most appropriate source for the real world figure when setting the baseline rate for repeat revascularisation without DES.	
British Cardiovascular Society and British Cardiovascular Intervention Society		***(b)*** *The relative risk of certain high risk groups* The worldwide literature repeatedly reports that patients with long lesions, small vessels and diabetes have a particular high risk of repeat intervention (relative excess risk of 1.75 for small vessels, 1.35 for long lesions and 1.52 for diabetes). We therefore believe that the correct figures for the risk of repeat revascularisation with a bare metal stent to be used in any model must be 22.8% for small vessels (from 1.75 x 13%); 19.8% for diabetes and 17.6% for long lesions. We presented this to the Committee as tables with references, and broken down into those studies that were angiographically driven and those where the repeat revascularisations were clinically driven. The Assessment group were encouraged to do something similar but perversely elected to use figures from the Liverpool database that, in stark contrast to the world literature, did not indicate any increased risk for these recognised as high risk groups. We have consistently argued that the Liverpool data are poor for this type of analysis and systematically biased against the high risk groups. These values are so vital to the subsequent cost effective analysis that we would urge NICE to revisit them using the worldwide literature. High risk patients (small vessels, long lesions, diabetics) have a 30% to 75% extra chance of requiring a repeat procedure as a result of recurrent symptoms. This was recognised in earlier guidance from NICE and justifies the use of drug eluting stents in these selected	The Appraisal Committee did not accept all the parameters and assumptions in LRiGs model see FAD sections 4.3.4, 4.3.5, 4.3.6, 4.3.7, 4.3.10, 4.3.11, 4.3.12, 4.3.13 and 4.3.14. The Appraisal Committee considered BCIS’s assumptions see FAD sections 4.2.23, 4.2.28, 4.3.13 and 4.3.14.

		patients.	
British Cardiovascular Society and British Cardiovascular Intervention Society		***(c)*** *The benefit of a drug eluting stent over a bare metal stent - what is the real reduction in need for subsequent revascularisation using DES?* After consulting the extensive published literature, we argued that DES reduced the chances of needing a repeat revascularisation by between 61-70%. Again, we presented the evidence for this in the form of a table with references. The committee eventually used a value of 55%; we can see no logic or explanation for the use of this figure other than compromise between the Liverpool Assessment Group nonsensically low original 35% reduction in need for repeat revascularisation and the published figures of 60%-70%. Use of unjustified compromise or averaging of values should clearly not be the basis for such an important assessment – the correct and published data should be used. The Assessment group argued that the effect of drug eluting stents was over-estimated by the angiographic follow up used in the randomised trials. The data we presented were based on trials and registries with and without angiographic follow-up so we fail to understand the Committee's position. Indeed, the Appraisal text contains figures that testify to the absolute benefit of DES - a one year reported TLR for BMS of ~20% and for DES ~5% - this equates to a 75% reduction, yet the figure of 55% is used with no explanation and for no apparent reason.	The Appraisal Committee did not accept all the parameters and assumptions in LRiGs model see FAD sections 4.3.4, 4.3.5, 4.3.6, 4.3.7, 4.3.10, 4.3.11, 4.3.12, 4.3.13 and 4.3.14. The Appraisal Committee considered BCIS's assumptions see FAD sections 4.2.23, 4.2.28, 4.3.13 and 4.3.14.
British Cardiovascular Society and British Cardiovascular Intervention Society		***(d)*** *The cost differential between drug eluting stents and bare metal stents.* We feel this is a crucial, but to date harder to clarify, part of the entire appraisal. Using our cost/efficacy model, which we based on that used by the Liverpool Assessment Group (and which we have confirmed as being "acceptable" by modelling in their figures and deriving their, albeit inappropriate, results) and populating it with the figures we have justified above we were able to show that a cost effectiveness of £30,000 per QALY could be met in small vessels, long	Comments noted. The Institute has received data from PASA for 2007/08; see FAD section 3.6.

		lesions and diabetes with a price "delta" of £491, £363 and £354, respectively. We believe that the current price premium of drug eluting stents within the NHS is below all three figures. The prices quoted by the Liverpool Assessment group and the committee are 2 years out of date and grossly inflated. The price for a Taxus stent (£815) and a Cypher stent (£937) used in the economic model therefore bear no resemblance to the true costs of these devices within the NHS price structure which are around £550 and £600. The suggestion used throughout the appraisal that Scotland has achieved a lower cost of drug eluting stents compared to the rest of the United Kingdom is simply not true. Furthermore, in February 2006 NICE reported that the Liverpool price differential of £500 was too high and that is likely to be nearer £300. This is quoted in a publicly available document. We believe the committee should seek up-to-date prices for DES within the NHS. BCIS have recently carried out just such a survey. The results are attached in Appendix 1 and show a "true" cost of DES in the NHS to be £550-600. In addition, 3 Scottish centres appear in the data and they are not the lowest 3 prices. We strongly believe that running the model with the true base rate for bare metal stent, true published benefit for DES and the true price difference will prove the cost efficacy of these devices.	
British Cardiovascular Society and British Cardiovascular Intervention Society		(iii) **Do you consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS**? We believe this cannot be the case and that using inappropriate data will lead to unsound recommendations. We believe the data used by the Liverpool Assessment group and the process of deriving the Committees conclusions should be subjected to **independent review.** In addition we believe that a **threshold analysis** should be undertaken, using	DESs are recommended in circumstances outlined in FAD section 1.1. The Appraisal Committee did not accept all the parameters and assumptions in LRiGs model see FAD sections 4.3.4, 4.3.5, 4.3.6, 4.3.7,

		the correct clinical data variables as outlined above, which will indicate the price premium at which DES <u>are</u> cost effective within the current pricing structure of the NHS. We believe that this derived price premium would in the circumstances of using correct data actually be in line with the real current cost of DES in the UK. Only by doing this could any Appraisal be a "suitable basis for the preparation of guidance to the NHS". A paradoxical effect of this unsound guidance will be to drive up the overall cost of coronary revascularisation to the NHS. If this draft appraisal is upheld clinicians will not return to the use of bare metal stents. They will use data from the ARTS1 trial and refer large quantities of patients back to cardiac surgery. This will result in increased morbidity to our patients, increased waiting times, failure to achieve Government driven targets, and a clear increased cost to the NHS. Our calculations suggest that >10,000 patients will be referred back to surgery at a cost of £60 million.	4.3.10, 4.3.11, 4.3.12, 4.3.13 and 4.3.14. The Appraisal Committee considered BCIS's assumptions see FAD sections 4.2.23, 4.2.28, 4.3.13 and 4.3.14.
Cordis		• The Evaluation Report and ACD do not take all relevant evidence into account with respect to DES price, absolute risk of repeat revascularisation, the risk reduction associated with DES and diabetes as in independent predictor of repeat revascularisation. • Cordis believe that the price premium of £600 stated in the ACD is too high and its origin should be clarified. This appraisal has also failed to appreciate the price dynamics in the medical device market that NICE does not face when dealing with many pharmaceuticals. • The absolute risk of revascularisation with BMS is understated at 11% for an unselected population. The true rate, based on the Scottish registry requested by the Appraisal Committee, is 12.9% in elective patients and 16.6% in those with acute coronary syndromes.	Comments noted. See responses to each of these points below.

		• The risk reduction used in the economic model is inconsistent with trial data. The trial-based risk reductions of 70% should be used. • Diabetes is not off label for Cordis's Cypher stent and diabetes should, consistent with the literature, be considered as an independent risk factor for repeat revascularisation. • New data show that o 70%, not 55% is the appropriate risk reduction. o The assumption of a common risk reduction across all DES is not valid. o There is a differential MI benefit, that is not fully captured in the current model due to an inappropriate time frame. • Patients with acute coronary syndromes (ACS) should be investigated as a population in which DES would be cost effective. Using the trial-based risk reduction of 70%, ICERs range from £19,878 to DES being dominant in different risk-factor groups within the ACS population. • The Decision Support Unit should be asked to ensure that all relevant and up-to-date information is taken into account and the economic model is updated accordingly.	
Cordis		**Introduction** On 1 August 2007, the Institute issued an Appraisal Consultation Document on the use of coronary artery stents in ischaemic heart disease. In section 1.1 of the ACD, NICE indicated that drug-eluting stents are not recommended for use in percutaneous coronary intervention in patients	Comments noted. The Assessment Group began working on this appraisal in 2005 therefore the Code of Practice for Declaring

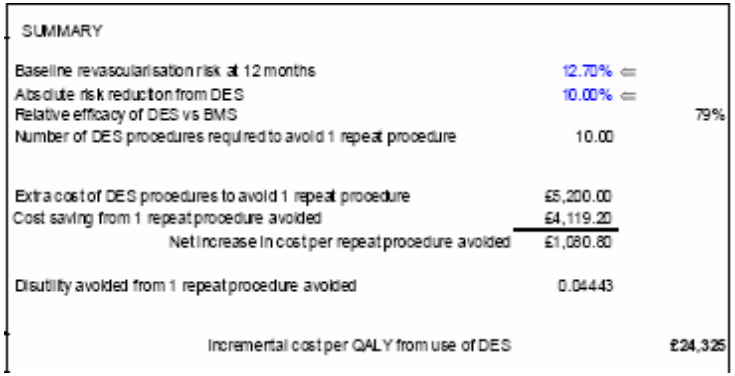
		with coronary artery disease. Cordis has a number of objections to the ACD, its recommendations, the Evaluation Report and the process upon which it is based. On numerous occasions, Cordis and other consultees have raised concerns about what they believe to be a clear and significant conflict of interest within the Assessment Group. In a paper published shortly before this Technology Appraisal, members of the Assessment Group published an economic assessment of DES (Bagust et al 2005). It has become increasingly clear that this publication has influenced its methods, assumptions and the manner in which it has selected clinical effectiveness data. These have often been inconsistent with the Institute's policies and procedures as set out in the Institute's Guide to the Technology Appraisal Process and Guide to the Methods of Technology Appraisal. The Institute has therefore prepared an ACD that is perverse in the light of the evidence submitted. Our detailed responses to the ACD are set out under five categories: • Has all the relevant evidence been taken into account? • Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence and are the preliminary views on the resource impact and implications for the NHS appropriate? • Are the provisional recommendations sound and do they constitute a suitable basis for the preparation of guidance to the NHS? • Are there any equality-related issues that may need special consideration? • Major new meta-analyses published and in press.	and Dealing with Conflicts of Interest does not apply to this appraisal. Previously the Institute has assessed the situation and concluded that there was no conflict of interest.

Cordis		**<u>Has all the relevant evidence been taken into account?</u>** ***In short, not all of the relevant evidence has been taken into account.*** The numerous submissions in the Evaluation Report show that consultees have repeatedly demonstrated that LRiG have consistently failed to present all the available evidence pertaining to: ▪ The DES price ▪ The absolute risk of repeat revascularisation with BMS ▪ The risk reduction associated with DES ▪ The risk factors for repeat revascularisation	Comments noted. See responses to specific points below.
Cordis		**<u>DES Price</u>** ***Cordis believe that the price premium of £600 stated in the ACD is too high and its origin should be clarified. This appraisal has also failed to appreciate the price dynamics in the medical device market that NICE does not face when dealing with many pharmaceuticals.*** This factor has clearly had a profound impact on the draft guidance, the implication of which is to potentially completely remove from the NHS, DES technology that has been in use for five years. It is unclear why £600 has been chosen as a DES price premium given that DES prices have fallen sharply over recent times, but we note that the original Assessment Report identified a premium of approximately £600. LRiG's market price survey is cited as May/June 2005 and is clearly out of date and irrelevant to guidance that will apply from 2008 onwards. It would be perverse for an inaccurate DES price to be used, particularly as experts have already given evidence that much lower prices are already available in the market. The reference to national procurement of DES in section 4.3.13 of the ACD is surely misplaced, as the Institute would be exceeding its powers if such a	Comments noted. The Institute has received data from PASA for 2007/08; see section 3.6.

		statement were perceived to be advising a procurement policy. The price issue is not straight forward, and raises a number of points unique to devices that the Institute does not often face with pharmaceuticals. Pharmaceutical prices tend to be reasonably constant over time during the period a drug has patent protection, and decrease only when generic competition is possible. Devices, on the other hand, do not benefit from long periods of market exclusivity. It is easier for a competitor to develop an alternative device to do the same job than it is for a drug company to find a new compound, and once the idea is in the public domain, the time to market is relatively short, compared with drugs. This results in much earlier competition, a shorter product life cycle, and greater market price competition. Average selling prices therefore fall more quickly than with drugs. This Review over-simplifies the market conditions for stents and a wider understanding of the market conditions is required. When BMS were the novel technology, introduced in the mid-1990s, the list price was of the first BMS to market (produced by Johnson & Johnson) was approximately £1,500. The first DES (Cypher, Johnson & Johnson) was introduced in 2002 again with a list price of £1,500, in real terms lower than the original BMS list price. In 1998-99, the mean market price for BMS in five UK hospitals was £582 (range £750 to £500) (Sculpher et al, 2002). At the time of the first stent HTA in 2000 (TA number 4), Meads et al (2000) reported list prices for BMS ranging from £650 to £1,440 and average selling price appeared to be around £500. The stent review in 2002 (TA no. 71) reported a cost for BMS of £341 whilst Jenkins et al (2002) reported a cost of £380 in the same year, giving an average of £361. The current Assessment Report gave a market average of £278. Thus, market prices of BMS always fall within a wide range, but overall, have fallen dramatically over time. The reality of the situation today is that the NHS is now procuring DES, and where necessary Clopidogrel,	

		for less than the cost of DES alone when the original guidance was produced in 2003. This fall in BMS prices has taken place at the same time as, and as a result of, falling DES prices. The Institute's methods must take account of these dynamics because the ICER as a binary decision-making tool becomes unreliable in this situation, despite the fact that the effectiveness of DES, as stated in the ACD, has not diminished. If device price dynamics were not taken into account, there would potentially be regression to the least expensive therapy even if it had already been rendered clinically obsolete in many patients. NICE needs to recognise that the market place for medical devices is different from pharmaceuticals, where patent protection does give market exclusivity and something closer to a monopoly supplier. To provide meaningful guidance to the NHS relating to medical devices NICE needs to recognise the difference between drug and device markets. NICE may find an acceptable solution to be use of average selling prices, as was the case in the first DES appraisal in 2003, or to use list prices as per its own Guide to the Methods of Technology Appraisal "*Where the actual price paid for a resource may differ from the public list price (for example pharmaceuticals, medical devices), the public list price should be used*" (NICE 2004, section 5.6.1.1). We recognise the desire from the NICE to quote a price that all NHS hospitals can procure at, but NICE should also recognise that not all providers purchase BMS at the same price now. Furthermore, it would be inequitable to use list prices as a source of upper DES price certainty whilst at the same time using market prices for BMS.	
Cordis		**The Absolute Risk of Repeat Revascularisation with BMS**	The Appraisal Committee

		The absolute risk is understated at 11% for an unselected population. The true rates, based on the Scottish registry and requested by the Appraisal Committee, are 12.9% in elective patients and 16.6% in those with acute coronary syndromes. The ACD states that the absolute risk of repeat revascularisation with BMS have been chosen to be 11% for all patients, based on 10% for elective patients and 13% for non-elective patients. It is not clear how these rates have been determined because the submission to NICE by NHS QIS (dated 13th January 2006) states: *"The Scottish Coronary Revascularisation Register Report for 2003-04 reports a repeat revascularisation rate at 12 months of 12.9% (95%CI 12.1-13.7; n=6525 vs 7.79% in Liverpool) for patients undergoing elective PCI and 16.6% (15.7-17.6; n=5921 vs 10.15% in Liverpool) for patients undergoing PCI for unstable coronary syndromes."* As the Appraisal Committee requested that the Scottish data be used to inform the base case scenario in the economic model (specification of additional work, February 2006), we would have expected this to be implemented. This is clearly a case where relevant evidence was identified by the Appraisal Committee, but is has not been taken into account in the economic model. It is perverse to specify use of a data input and then later ignore it. It is also of note that the 2003 Appraisal employed a BMS revascularisation rate of 12.7% (LRiG 2003 Addendum B, page 35), but this evidence appears to have been omitted from this Review. As there is no evidence that BMS repeat revascularisation rates have fallen since 2003, how can a reduction in the base case rate in the model be justified in this review? A copy of the relevant section	did not accept all the parameters and assumptions in LRiGs model see FAD sections 4.3.6, 4.3.12, 4.3.13 and 4.3.14 of the FAD. The Appraisal Committee considered BCIS's assumptions see FAD sections 4.2.23, 4.2.28, 4.3.13 and 4.3.14.

		of the 2003 model is reproduced in Figure 1:  SUMMARY Baseline revascularisation risk at 12 months 12.70% ⇐ Absolute risk reduction from DES 10.00% ⇐ Relative efficacy of DES vs BMS 79% Number of DES procedures required to avoid 1 repeat procedure 10.00 Extra cost of DES procedures to avoid 1 repeat procedure £5,200.00 Cost saving from 1 repeat procedure avoided £4,119.20 Net increase in cost per repeat procedure avoided £1,080.80 Disutility avoided from 1 repeat procedure avoided 0.04443 Incremental cost per QALY from use of DES £24,325 **Figure 1. Baseline risk and absolute risk reduction used in the 2003 Appraisal of DES.**	
Cordis		**<u>The Risk Reduction Associated with DES</u>** ***The risk reduction used in the economic model is inconsistent with trial data. The trial-based risk reduction of 70% should be used.*** We welcome the fact that the Appraisal Committee have recognised that a 41% reduction in repeat revascularisation risk under-estimates the effectiveness of DES, but the use of 55% risk reduction is still an under-estimate of the true treatment effect shown by the randomised trials. The use of a trial-based effect is recommended by NICE's own Guide to the Methods of Technology Appraisal, which states *".....RCTs are therefore ranked first in the hierarchy of evidence for measures of relative treatment effect."* It would be procedurally unsound and produce a perverse outcome for NICE to fail to follow its own methods guide.	The Committee did not accept all the parameters and assumptions in LRiGs model see FAD sections 4.3.4, 4.3.7, 4.3.12, 4.3.13 and 4.3.14. The Appraisal Committee considered BCIS's assumptions see FAD sections 4.2.23, 4.2.28, 4.3.13 and 4.3.14.

		The model should be re-run using a 70% risk reduction, as shown in Section 6 (a value that confirms the trial-based treatment effects used in Cordis's original submission). It is also notable that the 2003 Appraisal used 79% DES risk reduction (Figure 1), so it is unclear why the current economic model employs a risk reduction of 55%, given that the Appraisal Committee have recognised that the clinical benefit of DES has been sustained. Whilst the Assessment Group has continued to assert that the protocol-mandated angiogram in some of the randomised trials increases the DES treatment effect, there is no evidence for this. Schömig et al (2007) investigated this very question and concluded: *"10 of the 16 trials included in this meta-analysis had a **protocol-mandated follow-up angiography**. This may exaggerate the risk of the occulo-stenotic reflex and lead to an increase in the number of reinterventions, although **no significant interaction could be found between this study design feature and treatment effect**. In addition, the fact that the difference in the risk of reintervention between the 2 DES types persisted even beyond the scheduled time for follow-up angiography (6 to 9 months) **does not support a significant impact of protocol-mandated follow-up angiography on the treatment effect** in favour of the SES observed in this meta-analysis.* Thus, there is no need to dilute the trial-based risk reductions due to concerns over the impact of the trail angiogram.	

Cordis		**<u>Risk Factors for Repeat Revascularisation</u>** ***Diabetes is not off label for Cordis's Cypher stent and diabetes should, consistent with the literature, be considered as an independent risk factor for repeat revascularisation.*** We recognise that the Appraisal Committee has accepted long lesions and small vessels as risk factors for repeat revascularisation. The ACD suggests in section 4.3.4 that there is still some doubt over diabetes as an independent risk factor for repeat revascularisation. This conclusion is perverse in the light of evidence submitted. Cordis's response to the Assessment Report Addendum presented seven studies not cited by LRiG, five of which identified diabetes as an independent predictor, along with two others previously identified. Of the 14 literature sources identified, diabetes was the second most commonly occurring independent risk factor (in 7 out of 14 datasets). It is remarkable that this evidence from the entire literature has not prompted a clear statement that diabetes is an independent predictor of repeat revascularisation. In the latest cost effectiveness analysis (Addendum 6') LRiG have used an unusually low relative risk (RR) for diabetes (1.19). This results from the sole reliance on the CTC database and a combination of relative risks of 0.90 for non-elective patients and 1.38 for elective patients (Addendum 4'). It is notable that the British Cardiovascular Intervention Society (BCIS) have adopted a more reasonable approach in their response to Addenda 3'' and 4', in deriving relative risks from the wider literature. BCIS identify a RR of 1.52 for diabetes (range 1.34 to 1.81) and LRiG should have noticed that in comparison, the CTC dataset has produced an apparently spurious result that is driven by the peculiar RR of 0.90 for non-elective patients. It is most odd to quote a RR of <1 for a risk factor that has been shown to increase the relative risk and is perverse in the	With regard to diabetes as a risk factor see FAD sections 4.1.23, 4.1.24 and 4.3.4. The Appraisal Committee considered BCIS's assumptions see FAD sections 4.2.23, 4.2.28, 4.3.13 and 4.3.14.

		light of the other evidence submitted. This is a clear example of LRiG failing to take all the relevant evidence into account and it would be more reliable to run the economic used to produce Addendum 6' (that informed the ACD) using the BCIS mean relative risk of 1.52. LRiG's relative risks for the individual risk factors of small vessels and long lesions are within the ranges in the wider literature and on that basis, although somewhat low for long lesions, seem reasonable.	
Cordis		**Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence and are the preliminary views on the resource impact and implications for the NHS appropriate?** ***The summaries of clinical and cost effectiveness are not reasonable on the following grounds:*** The source of the DES price information is unclear, but appears to be 2 years out of date. It is therefore an unreasonable interpretation of the resource impact for the NHS. The absolute risk of repeat revascularisation has been unreasonably reduced compared with the rates submitted from the Scottish registry and that used in the original DES appraisal. The risk reduction associated with DES has been unreasonably reduced compared with the rates from the randomised trials.	Comments noted. The Appraisal Committee did not accept all the parameters and assumptions in LRiGs model see FAD sections 4.3.4, 4.3.6, 4.3.7, 4.3.10, 4.3.11, 4.3.12, 4.3.13 and 4.3.14. The Appraisal Committee considered BCIS's assumptions see FAD sections 4.2.23, 4.2.28, 4.3.13 and 4.3.14.
Cordis		Removal of DES from the NHS will have an undoubted effect on NHS service provision in that some patients who may currently be treated by PCI with DES will in future need to be referred to CABG because the restenosis risk with BMS will simply be too great. The potential impact can be estimated as follows:	DESs are recommended in circumstances outlined in FAD section 1.1.

		58,576 PCIs in England and Wales in 2005 (Ludman 2006) models to 67,809 PCIs in 2008, assuming a conservative growth of 5% per year. If 20% of these patients are referred back to CABG, surgical capacity has to increase by 13,562 procedures from a standing start in 2008. Bearing in mind that there were 22,724 CABG procedures in 2005 and CABG has not shown growth, this equates to a potential demand for a 40% increase in CABG. In addition, the CABG reference cost, at weighted average of £8,198, is 2.54 times than PCI with DES at £3,231. This cost differential means that the NHS will have to pay an extra £67.4 million to achieve the same number of revascularisation procedures. In addition, the NHS will also have to fund an additional 4,231 repeat revascularisation procedures (based on the current LRiG model) at a cost of £16.2 million. Thus, the gross cost would be approximately £83.5 million. Assuming current DES usage of 60% and an incremental cost of £870 per DES procedure (LRiG model), the cost avoided if this draft guidance becomes final would be £28.3 million. The net cost to the NHS is therefore likely to be £55.2 million in 2008 alone. The ACD does not take these costs and service implications into account and this estimate takes a conservative view of the potential shift back to surgery.	
Cordis		**Are there any equality-related issues that may need special consideration** Diabetic patients are not 'off label' for the Cypher stent in Europe. Diabetes is not a contra-indication on the Instructions for Use. Section 4.1.24 of the ACD should be removed as it constitutes unfounded inequality towards diabetic patients on the basis and the Institute is exceeding its powers in pronouncing diabetics to be off label. We believe diabetic patients should be mentioned as a specific high-risk group who should benefit from DES.	DESs are recommended in circumstances outlined in FAD section 1.1. With regard to diabetes see FAD sections 4.1.23, 4.1.24, and 4.3.4.

Cordis		**<u>Recommended Solutions</u>** The economic model should be updated to addresses all the concerns identified above. At a minimum, it must incorporate and address: An accurate absolute risk of repeat revascularisation from the Scottish registry. The NHS QIS submission dated 13th January 2006 (in the Evaluation Report) shows this to be 12.9% (elective) and 16.6% (ACS patients) for unselected populations without protocol-mandated angiographic follow up. A literature-based relative risk of 1.52 for diabetes. LRiG's relative risk of 0.90 for non-elective patients is clearly unrepresentative and makes their relative risk for all diabetics unrealistically low (outside the range seen in the wider literature quoted by BCIS). A repeat revascularisation risk reduction of 70%, based on the randomised trials – see Section 6. An extended time horizon as the current 1-year time does not capture the full benefit of the Cypher stent, particularly in the light of the new data on MI benefit shown in Section 6. The Institute's Guide to the Methods of Technology Appraisal requires the selection of a time horizon "sufficient to reflect important cost and benefit differences between the technologies being compared" (section 5.2.1.1), thus the time horizon should be extended to capture the full impact of the MI benefit. Acute coronary syndromes (ACS) as a patient sub-group. Whilst clinical experts have advised that 'elective' and 'non-elective' are not appropriate term to distinguish between patient groups, patients with ACS are a recognised sub-group and this is alluded to in section 4.3.5 of the ACD. This is also recognised in the Institute's recent announcement of the development of a clinical guideline	Comments noted. The Appraisal considered BCIS's assumptions see FAD sections 4.2.23, 4.2.28, 4.3.13 and 4.3.14. The Appraisal Committee considered a one year time horizon to be appropriate see FAD section 4.3.6. The Appraisal Committees considerations of this point is described in FAD section 4.3.10.

<table>
<tr><td></td><td></td><td>for patients with ACS. The Appraisal Committee should be mindful that DES would be cost effective in at least some ACS patients because there is no additional Clopidogrel cost. The Appraisal Committee should also note that the repeat revascularisation rate in an unselected population is 16.6% at 1 year according to the NHS QIS submission. Non-elective costs, resource use and relative risks are most appropriate for this group of patients, as they tend to present as non-elective PCI. This issue deserves some exploration, but correct and representative data should be used as model inputs, as outlined by consultees throughout this process.</td><td></td></tr>
<tr><td>Cordis</td><td></td><td>Table 1 shows the impact of substituting a trial-based risk reduction of 70%, relative risk of 1.52 for diabetes and DES price premium of £390 into a reproduction of LRiG's model for ACS patients. Even using the £600 price premium, with which we profoundly disagree, most of the risk factor groups are cost effective for ACS patients.

<table>
<tr><th>Risk Factors</th><th>ICER</th></tr>
<tr><td>No risk factors</td><td>£33,140</td></tr>
<tr><td>Long lesions</td><td>£19,878</td></tr>
<tr><td>Diabetes</td><td>7,166</td></tr>
<tr><td>Small vessels</td><td>DES dominant</td></tr>
<tr><td>Long lesions + diabetes</td><td>£32,640*</td></tr>
<tr><td>Long lesions + small vessels</td><td>DES dominant</td></tr>
<tr><td>Small vessels + diabetes</td><td>DES dominant</td></tr>
<tr><td>Long lesions + small vessels + diabetes</td><td>DES dominant</td></tr>
<tr><td>Overall</td><td>£30,790</td></tr>
</table>

Table 1. ICERs by risk factor for patients with acute coronary syndromes. ICERs calculated using a</td><td>Comments noted.</td></tr>
</table>

		*reconstruction of the LRiG model but with risk reduction of 70%, literature based relative risk of 1.52 for diabetes and DES premium of £390. * = unreliable result due to use of LRiG relative risk for patients with combined risk factors of long lesions and diabetes, where LRiG's diabetes risk is spurious.*	
Cordis		The Evaluation Report shows that consultees have repeatedly demonstrated LRiG 's failure to present the Appraisal Committee with all the relevant evidence on many occasions. These failures may well be due to the LRiG's unwillingness to contradict their pre-formed opinion on the cost effectiveness of DES, published prior to the deadline for submissions by consultees. Given the clear and documented problems that this has created throughout, we call for this Review to be referred to the **Decision Support Unit** to ensure that all relevant and up-to-date information is taken into account.	The Committee did not accept all the parameters and assumptions in LRiGs model see FAD sections 4.3.4, 4.3.5, 4.3.6, 4.3.7, 4.3.10, 4.3.11, 4.3.12, 4.3.13 and 4.3.14. The Appraisal Committee considered BCIS's assumptions see FAD sections 4.2.23, 4.2.28, 4.3.13 and 4.3.14.
Department of Health		Cost effectiveness of DES Whether DES are cost effective depends on the relative risk reduction in revascularisations and the absolute rate of revascularisation (para 4.2.14). According to the ACD the absolute rates of revascularisation are derived only from the Liverpool Cardiothoracic Centre (CTC) audit data. We have a number of concerns about the use of this single source of data.	Comments noted. The Appraisal Committee was aware of the views expressed by consultees and commentators about the CTC database. Therefore it did not accept all the parameters and

		We have data on revascularisation rates for the former Cheshire and Mersey SHA for which Liverpool CTC is the only cardiac centre. These show that Liverpool CTC is a significant outlier: • In 2005/6, Cheshire and Mersey SHA had the lowest revascularisation rates per million population in the country and this has changed relatively little since 2001/2 (see slides 2 and 3 attached). • The rates of coronary artery bypass graft (CABG) per million has stayed about the same between 2001/2 to 2005/6 where most areas have a reduced rate because of increases in the use of stents (see slides 4 and 5 attached). • Cheshire and Mersey SHA had the lowest rate of Percutaneous Coronary Intervention(PCI) per million in the country in 2005/6 and the fourth lowest rate of change in PCI rate since 2001/2 (see slides 6 and 7 attached) • Cheshire and Mersey had the second lowest ratio of PCI to CABG in the country in 2005/6 at 1.5 : 1 (see slide 8 attached). For example it might suggest that complex cases are referred for CABG in Liverpool CTC whereas in other places DES are used which would be less costly than referring for CABG. The attached slides provide information of other centres. Would the Appraisal Committee be able to consider data from other centres and revisit its assumptions on revascularisation rates used in its costing model? A second point on cost effectiveness is the variation in cost per QALY in the ten economic evaluations (para 4.2.1 to 4.2.7) compared to the Assessment Group model (para 4.2.23). It would be helpful to understand what factors contribute to this significant difference please.	assumptions in LRiGs model see FAD sections 4.3.4, 4.3.5, 4.3.6, 4.3.7, 4.3.10, 4.3.11, 4.3.12, 4.3.13 and 4.3.14. The Appraisal considered BCIS's assumptions see FAD sections 4.2.23, 4.2.28, 4.3.13 and 4.3.14.
Department of		Consequences of implementing the recommendation	DESs are recommended

Health		The ACD accepts the consequence of increased revascularisation procedures in long lesions and small vessels (Para 4.3.2 and para 4.3.7) and the relative risk reduction of DES of 55-65% (para 4.3.7). Does this mean that there will also be increased morbidity if only Bare Metal Stents (BMS) are available? What consideration has the Appraisal Committee given to this? In our view interventional cardiologists are likely to refer significantly more patients for CABG, in view of the evidence base for BMS in high risk cases, and the ACD acknowledges the morbidity, mortality and 'disutility' of CABG (Page 30). As a consequence waiting lists for CABG are likely to increase and associated service delivery costs (procedural, in-hospital waits etc.) will rise. Those factors will make it more difficult to achieve the 18-week target. Has the Appraisal Committee taken account of these points?	in circumstances outlined in FAD section 1.1.
Department of Health		Diabetes Could you please consider including diabetes as a risk factor for restenosis.	At the time of the last Appraisal Committee meeting, none of the DESs was specifically licensed for people with diabetes. The Institute did not receive instructions from the Department of Health to include off label use. The Appraisal Committee took note of the view of the regulatory agencies and the FAD was updated with recent changes to the licences. See FAD sections 4.1.23, 4.1.24 and 4.3.4.

Department of Health		Review date We think that it may be beneficial if an earlier review date than January 2011 was set because important clinical trials, such as SYNTAX, will report over the next 18-24 months. SYNTAX is a large multi centre randomised trial of PCI versus CABG and it is likely that this study will establish the standard to guide revascularisation decisions for patients with extensive coronary artery disease for the foreseeable future. Principal results will be reported in Autumn 2008.[1]	The review date has been changed accordingly.
DHSSPSNI		Based on currently available randomised clinical trial data the benefit of drug eluting stents (DES) over bare metal stents is reduction in need for re-intervention due to in-stent restenosis (ISR). It is clear from randomised clinical trial data and from clinical practice that benefits are greatest in patients with small vessels (<3.0mm, particularly 2.25 - 2.5mm), and long lesions. Diabetes is an additional risk factor for ISR although such patients are typically already identified at higher risk given their smaller vessel calibre and/or diffuse disease necessitating longer stent length. Experienced high volume interventional cardiologists recognise the futility in deploying long lengths of small calibre bare metal stents in clinical practice as they almost invariably restenose. Such data are only partly represented in clinical trials but are well recognised in clinical practice. Thus in the past, many patients deemed as unsuitable for bypass surgery (due to inadequate target vessel calibre) were also deemed unsuitable for stenting. With the advent of DES, such patients can now be offered revascularisation with acceptably low risk of ISR, often gaining symptom relief after years of angina, being able to stop many of their multiple anti-anginal medications and avoiding need for repeated costly primary and secondary care reviews. Not infrequently patients may even	Comments noted. DESs are recommended in circumstances outlined in FAD section 1.1.

[1] Editorial comment : Left Main DES, Stone et al , Journal of the American College of Cardiology 2007:50;498-500

		be able to return to work after a lengthy period of sickness absence. The true costs to society and to the individual of not offering revascularisation/small vessel stenting because of perceived risk of target vessel failure are thus substantial but are not addressed either in clinical trials or in local audits such as the Liverpool CTC study.	
DHSSPSNI		Much of the focus of subsequent BCIS correspondence to the original draft has been to debate true percentage need for re-intervention, the real rather than list price premium for DES, and clopidogrel duration in practice. It is not necessary to reiterate these or other than to state that Northern Ireland experience broadly concurs with BCIS comments.	Comments noted. See responses to BCIS's comments.
DHSSPSNI		The key issue for this guidance is its clinical credibility among practising interventionists in order to achieve consistent standards of clinical effectiveness throughout England, Wales and Northern Ireland. The current draft effectively recommends a step back to bare metal stenting for long length, small calibre vessels which is clinically untenable. From a Northern Ireland perspective, the committee is thus urged to revise the draft so that the final document is of optimum benefit in guiding best contemporary clinical practice.	DESs are recommended in circumstances outlined in FAD section 1.1.
Clinical expert		Having considered all of the evidence contained within this document I am concerned that this appraisal is entirely focused on the financial impact of drug eluting stents on the service and may produce a major retrograde step in practice as a consequence of questionable assumptions. As an experienced NHS manager and senior nurse I recognise the cost pressure this form of treatment generates in the short term. However, whilst I recognise it may be a small group of patients, the long term cost implications in both financial and psychological terms for the patient must be recognised.	Comments noted. The Appraisal Committee does not consider the affordability, that is costs alone, of new technologies but rather their clinical and cost effectiveness in terms of how its advice may enable the more efficient use of available healthcare resources (NICE Guide to the Methods of

			Technology Appraisal, paragraphs 6.2.6.1 – 6.2.6.3).
Clinical expert		I am unsure that all relevant information has been considered. Whilst there has clearly been extensive and comparative research studies, from my perspective, the focus on mortality as the primary outcome has overridden the focus on quality of life and a positive experience for the patients affected.	Comment noted. Mortality was not considered as primary outcome in this appraisal, instead he focus was on total revascularisation rates and quality of life.
Clinical expert		I can not agree that the resource impact and implications for the NHS are appropriate as there does not seem to be consideration of the cost implications of practice changes which will accrue as more patients are driven to CABG by concern regarding the requirement for further procedures..	Comment noted. DESs are recommended in circumstances outlined in FAD section 1.1.
Clinical expert		I would question whether this proposal is sound as it is overly proscriptive and would have considerable governance implications for both patients and clinicians as it excludes the clinician's ability to administer the best possible treatment for each patient as an individual. This may have detrimental effect on the care of patients at higher risk of restenosis.	DESs are recommended in circumstances outlined in FAD section 1.1.
Clinical expert		Whilst I recognise from my considerable clinical experience that drug eluting stents are not always appropriate, there are groups of clearly defined patients in the higher risk bracket that ethically, morally and financially would benefit from the treatment.	DESs are recommended in circumstances outlined in FAD section 1.1.
Clinical expert		I also recognise the need to provide cost effective, evidence based care to all groups of patients, this change in practice would have a detrimental effect to the patient and the NHS. If the committee believe that this must be enforced I would strongly advise the high risk groups are exempt.	DESs are recommended in circumstances outlined in FAD section 1.1.

KiwiMed	2.8	I would like to draw your attention to wording in the evaluation report section 2.8 as below: ***Other than one trial (the ELUTES trial), there is little evidence to support coating the stent directly with an active drug (without a polymer).*** Our non Polymer YUKON DES has been in use now for 5 years with clear clinical outcomes that do verify it's equivalence with polymer based DES. The ISAR TEST study (attached) for example, clearly showed our equivalence with the Taxus stent in late lumen loss and restenosis.	Comment noted. As the issue of polymer versus non-polymer stents has not been covered in this review, this wording has been removed accordingly.
KiwiMed		**Anti platelet therapy** The other cost factor influencing the financial viability of using DES over BMS is that of long term anti-platelet therapy. Although the reasons for the increase of late thrombosis in drug eluting stents is still unclear it is generally accepted that this long term safety issue was not apparent with BMS. In regard to increase in anti platelet therapy with DES your appraisal took account of this additional 9 months of Clopidogrel cost however generalised that all DES required 12 months anti-platelet therapy. Due to the unique nature of the Yukon DES we will shortly be in a position to recommend the same anti platelet therapy as prescribed for patients receiving BMS's and should receive recognition for this cost saving in your appraisal. The Harefield and Royal Brompton Hospital Trust are just completing a study looking at endothelisation of the stent struts of the Yukon in comparison with the Cypher. The early coverage of stent struts is generally accepted to be a good surrogate indicator for long term safety and will allow for reduced anti-platelet therapy. The outcome data from this study will be published shortly.	The Appraisal Committees considerations of this point are described in FAD sections 4.1.22 and 4.3.10.
KiwiMed		**Price premium**	The Institute has received data from PASA for

		It is clear that much of the DES and BMS pricing that has been used in the assessment groups model is now out of date and if reviewed in light of price changes over the past year many of the available DES's would fall within the price premium bracket of £300 making them price effective in patients with small vessels and long lesions. The pricing on the Yukon DES has always fallen under this recommended price premium.	2007/08; see FAD section 3.6.
Patient expert		**Do you consider that all the relevant evidence has been taken into account?** I am very concerned that the British Cardiac Society do not feel that this is the case and I feel that their views should be considered very carefully before finalising this guidance. I feel the guidance in its current form would leave cardiologists in a very difficult position where they are forced to deliver less than optimal therapy, and that this will have a very demoralising effect on both the doctors and their patients.	Comments noted. DESs are recommended in circumstances outlined in FAD section 1.1.
Patient expert		**Do you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence and the preliminary views on the resource impact and implications for the NHS are appropriate?** I do not feel in a position to comment on the validity of the summaries but, once again, I am very concerned that the British Cardiac Society do not feel that the economic analysis is sound and I feel that their views should be considered very carefully before finalising this guidance.	Comments noted. The Committee considered BCIS's assumptions see FAD sections 4.2.23, 4.2.28, 4.3.13 and 4.3.14.
Patient expert		**Do you consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS?**	Comments noted. DESs are recommended in circumstances outlined

		No, I do not. Whilst I have no argument with your data I do not think that the figure of £600 can determine the treatment that individuals receive. We need to be pro-active and get the cost of Drug Eluting Stents reduced rather than just accepting an inferior level of service. How does Scotland and the rest of Europe manage to afford them?	in FAD section 1.1.
Patient expert		**Are there any equality related issues that may need special consideration?** Yes, there are. The proposal to introduce, what is effectively a two tier system, i.e. those who can afford to pay and those who have paid through their national insurance contributions, is totally unacceptable.	Comments noted. DESs are recommended in circumstances outlined in FAD section 1.1.
Medtronic		Thank you for the opportunity to comment on the addendas to the Assessment report. Whilst we appreciate that some minor amendments have been made to the economic model following requests/recommendations made by the Appraisal Committee and the cross industry working group since the appraisal committee meeting and industry response, we believe there to be some significant outstanding issues. We would like to address our concerns around three key areas: 1. Responsiveness of the LRiG group to requests for reanalyses/data selection 2. New data available to the group since the original submission deadline (July 2005) 3. The impact of the new data on the cost-effectiveness of Drug Eluting Stents (DES)	Comments noted.

Medtronic		**Responsiveness of the LRiG group to requests for reanalyses/data selection** Appendix 1 tabulates the NICE project specification table provided to the LRiG group regarding further work to be undertaken on the original assessment report economic evaluation. The table has been annotated with comments from Medtronic re actions taken by LRiG to address the appraisal committee's concerns. For example, it is perverse, that despite direct requests for LRiG to use data to assess risk factors for repeat revascularisation from alternative sources, LRiG have failed to do so and have continued to rely on single centre CTC audit data. Similarly, whilst Medtronic appreciate the incorporation of diabetes in the model as an independent risk factor, continued reliance on the CTC data to derive diabetes risk factors is unacceptable, as it is not representative of repeat revascularisation rates and underpowered to detect a difference in revascularisation rates between diabetics and non-diabetics. Furthermore, Table A6.2 *"Summary of risk model factors in reviewed papers"* does not present the results of a further 7 risk models, 5 of which identify diabetes as an independent risk factor for repeat revascularisation. These are but two examples (please refer to Appendix 1 for full listing) where it appears the wishes of both the appraisal committee and industry have been blatantly disregarded with no rationale given for LRiGs decisions. We strongly believe that from the outset, the LRiG have been unable to make rational decisions due to a conflict of interest. Medtronic would like to refer to their letter of 7th June 2005 written to Professor Sir Michael Rawlins to express concern regarding the believed conflict of interest of the Liverpool assessment group. As outlined, two members of the assessment group (Professor Bagust	Comments noted. The Appraisal Committee was aware of the views expressed by consultees and commentators about the CTC database. Therefore it did not accept all the parameters and assumptions in LRiGs model see FAD sections 4.3.4, 4.3.5, 4.3.6, 4.3.7, 4.3.10, 4.3.11, 4.3.12, 4.3.13 and 4.3.14. The Appraisal Committee considered BCIS's assumptions see FAD sections 4.2.23, 4.2.28, 4.3.13 and 4.3.14. Regarding diabetes see FAD sections 4.1.23, 4.1.24 and 4.3.4.

		and Professor Walley) published an article prior to the deadline for submission to this review which concluded that the technology could not be considered cost effective. We did not believe, and continue not to believe that members of the Liverpool group can be impartial under these circumstances. The LRiGs continued insistence that their approach is correct despite it conflicting with the clinical and economic findings of other published literature on DES calls into question the fairness of this appraisal. In the Code of Practice for Declaring and Dealing with Conflicts of Interest Issue published in April 2007 section 3.5 states: 3.5 **A personal non-pecuniary interest** in a topic under consideration might include, but is not limited to: i) a clear opinion, reached as the conclusion of a research project, about the clinical and/or cost effectiveness of an intervention under review ii) a public statement in which an individual covered by this Code has expressed a clear opinion about the matter under consideration, which could reasonably be interpreted as prejudicial to an objective interpretation of the evidence It is clear that the Institute, rightly understand the need for such a code and that should this code have been in existence at the beginning of this appraisal LRiG could not have been selected as the assessment group for this appraisal as their publication record can clearly be interpreted "as prejudicial to an objective interpretation of the evidence". We ask, that in the interests of fairness, this point is raised at the next appraisal committee meeting as a matter of priority in addition to a discussion on the potential role of the DSU in this appraisal.	Comments noted. The Assessment Group began working on this appraisal in 2005 therefore the Code of Practice for Declaring and Dealing with Conflicts of Interest does not apply to this appraisal. Previously the Institute has assessed the situation and concluded that there was no conflict of interest.
Medtronic		**New data available to the group since the original submission deadline**	Comments noted.

		(July 2005) As you are aware, due to significant delays in this guidance review, almost two years have passed since industry have been able to submit any new available data to the Institute for inclusion in the appraisal. Further to letter received by the Institute on 12 March 2007 where we were incorrectly informed that Medtronic would have the opportunity to submit additional data to the Institute, Medtronic prepared a brief summary of new data available which we believe should be drawn to the attention of the appraisal committee (please refer to appendix 2). Whilst we realise that this will not be formally included into the assessment report we would like some key messages to be conveyed to the committee: The Endeavor clinical program continues to generate strong cumulative evidence regarding Endeavor's overall performance, with consistent and predictable patient outcomes sustained over time. ***Indeed, the growing volume of positive data and number of patients with long-term follow-up continues to demonstrate the deliverability, the clinical efficacy and the strong safety profile of the Endeavor drug-eluting stent.*** The two-year results from the Endeavor III (EIII) trial confirms the positive clinical profile of the Endeavor drug-eluting coronary stent and bring to nearly 1,300 the number of Endeavor patients who have at least two years of follow-up. In EIII, at two years, the rate of Major Adverse Cardiac Events - a composite safety measure of death, repeat procedures and myocardial infarction (MI) – is 9.3% for Endeavor and 11.6% for the Cypher stent (p = 0.47). There is no statistically significant difference in the need for repeat procedures, or Target Lesion Revascularization (7.0% and 4.5% for Endeavor and Cypher, respectively, p = 0.50), or all-cause mortality (1.6% for Endeavor and 4.5% for Cypher, p = 0.14**). *However, fewer patients experienced heart attacks (MI)***	The process for submitting new evidence after the deadline for submissions is described in section 4.5.2.10 of the technology appraisal process guide. This process was not followed. With regard the extended use of clopidogrel see FAD sections 4.1.22 and 4.3.10.

		when treated with the Endeavor stent (0.6% vs. 3.6% for Cypher, p = 0.04) and the combined rate of heart attack and death also is statistically significantly lower among patients randomized to the Endeavor stent (2.2% vs. 7.1% for Cypher, p = 0.013). The reported pooled safety and efficacy data at one year on more than 1,300 patients from the Endeavor I, II, and III trials (including Endeavor II Continued Access) also confirms ***Endeavor's excellent safety record, with no observations of late stent thrombosis (more than 30 days after implant), and an overall thrombosis rate of just 0.3%. It demonstrates no significant differences in TLR or late loss across high risk subgroup parameters, such as vessel diameter size, lesion length and patient diabetic status.*** The 3-year data from the 100-patient first-in-man Endeavor I (EI) clinical study, and the 2-year results from the 1,200-patient, double-blind randomized Endeavor II (EII) pivotal trial, with a patient follow-up for both trials of 97%, show low rates of restenosis and an excellent safety profile. At 36 months, the combined rate for myocardial infarction, death and TLR in the EI study is 6%, while the 24-month MACE rate in EII is 10%. In EII, 93.5 percent of the Endeavor patients remain free of repeat procedures after two years, with a TLR rate of only 6.5 percent. In addition, in the ***EII study, there is no difference in mortality between the Endeavor (2.1%) arm and the Medtronic Driver (2.2%) bare metal stent arm, and the study also shows a 47 percent reduction in MACE between Endeavor arm (10.0%) and the Driver arm (18.7%).*** ***As a final point, Endeavor is safe by definition, when using either the definition of stent thrombosis used by the clinical trial HRCI CEC , or re-adjudicated expanded ARC stent thrombosis definition, or even simply the composite rate of death and Q-wave MI.***	

		Concerning the ARC reclassification and in terms of cumulative incidence out to three years, proportionally more events were added in the bare metal stent groups than in the Endeavor DES groups; the difference in event rates was significant (1.0% vs 3.3%; P = 0.01). The overall increase is driven mostly by increased late and very late 'possible' events, with definite or probable events similar to prior reports using protocol definitions and trending lower for the DES arm. The update on the safety data is especially pertinent to the Endeavor stent in this appraisal. In your communication of 11th April 2007, you stated that with respect to the economic modelling "Following the recent concerns over the safety of DES these sensitivity analyses have been extended to examine how the difference in the duration of clopidogrel use between BMS and DES may affect the cost effectiveness (see attached, Addendum 4'). This reflects recommendations made by the American Heart Association and the British Cardiovascular Intervention Society, that the duration of use of anti-platelet therapy (aspirin and clopidogrel) should be extended in patients who have received a DES to at least 12 months, and in particular in those patients whose lesions are thought to be high risk". What the Institute failed to mention was that the FDA and BCIS recommendations were made on the basis of three studies (Camenzind, Nordmann and Wenaweser) none of which include Endeavor related safety data. In Medtronic's current IFU, it states that "In clinical trials of the ENDEAVOR stent, clopidogrel or ticlopidine was administered pre-procedure and for a period of at least 12 weeks post-procedure. Aspirin was administered concomitantly with clopidogrel or ticlopidine and then continued indefinitely to reduce the risk of thrombosis". In view of this shorter duration of clopidogrel usage, the lack of data to show safety concerns associated with the Endeavor DES and the FDA statement that	

		"The optimal duration of antiplatelet therapy, specifically clopidogrel, is unknown and DES thrombosis may still occur despite continued therapy", may we strongly suggest that sensitivity analysis is conducted at a range of clopidogrel administration doses.	
Medtronic		**The impact of the new data on the cost-effectiveness of Drug Eluting Stents (DES)** In view of the new information available on the long-term efficacy and safety of Endeavor stent, we have re-analysed the cost-effectiveness model comparing the Endeavor stent to the Driver stent which was also included in the original submission. The model used the same inputs and assumptions as LRiG's model with the exception of using TVRs instead of total revascularisation rates and a longer time-horizon. Instead of extrapolating the observed 9-month outcomes from the Endeavor II trial to one year and then assuming that no difference exists between Endeavor and Driver between years 2 and 5, the up-dated model now relies on observed trial outcomes at 24 months pooled from the Endeavor II and Endeavor III trials. All other model inputs and assumptions remained the same. The trial evidence of sustained effectiveness had a favourable impact on the cost-effectiveness of the Endeavor stent versus the Driver stent with an incremental cost-effectiveness ratio below £10,000/QALY gained at 5 years. The results were also confirmed in a probabilistic analysis which showed Endeavor to have a 76% and 86% probability of being cost-effective compared to Driver, using a £20,000/QALY and a £30,000/QALY threshold, respectively.	Comments noted. See FAD section 4.3.3 for the Appraisal Committee's consideration of the comparisons between different types of DESs.
Medtronic		In summary, we have significant outstanding concerns regarding the actions of the LRiG in this appraisal. These concerns were raised early in the process and	Comments noted. See responses for Medtronic's

		have been consistently relayed to the Institute. Since our manufacturers submission there has been a significant increase in the availability of both clinical and safety data on Endeavor which translates into a strong cost-effectiveness argument for the use of this product in the NHS. We submit this response alongside the cross-industry response from BCIA with which, in the main, we are in concurrence. With respect to section 4.1 of the BCIA response, we kindly request that you also refer to section two of the Medtronic response regarding the duration of clopidogrel administration.	specific comments above.
NHSQIS Reviewer 1		Whether you consider that all the relevant evidence has been taken into account. No. Although alluded to in para 4.3.13 the economic evidence does not take into account the discounted prices negotiated through central procurement in Scotland (National Services Scotland National Procurement Contract no SFD036). The premium achieved in Scotland (the difference between whole systems costs of BMS and DES, though not taking into account the additional 9 month costs for Clopidogrel in non STEMI ACS patients) is £450, which is significantly less than the £600 premium used as the assumption by the analysts in para 4.1.11. This saving, brought about by binding commitment contracts, may bring the premium to the threshold for economic advantage of DES over BMS. Para 4.2.1 indicated that the price assumption was based on a market survey of NHS purchasers carried out by the NHS Purchasing and Supply Agency in May/June 2005 – the Scottish prices were concluded in September 2006 and hence update the evidence upon which the price assumptions were based.	The Institute has received data from PASA for 2007/08; see FAD section 3.6.
		Whether you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence. We would point out that procurement involves the entire interventional cardiology community in Scotland who contributed to the clinical evidence	

		section of the commodity score sheet. This Scottish clinical community has also contributed to the statement of the British Cardiovascular Intervention Society, submitted as consultation evidence.	
NHSQIS Reviewer 1		Whether you consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS. Not for the NHS in Scotland for the reasons stated above. A fresh contracting process for both BMS and DES is currently underway, which, again, is involving the whole of the Scottish interventional cardiology community. The results of this should provide cost-effective benefits to Scottish patients.	Comments noted.
NHSQIS Reviewer 1		Whether you consider that there are any potential policy implications for SEHD? Yes. Different prices north and south of the border could result in political sensitivity if the guidelines are published unchanged and adopted in Scotland, in the light of the points made above.	DESs are recommended in circumstances outlined in FAD section 1.1.
NHSQIS Reviewer 2		Whether you consider that all the relevant evidence has been taken into account. *As far as I know, the evidence has been taken into account. Whether there is enough evidence was highlighted.*	Comment noted.
NHSQIS Reviewer 2		Whether you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence. *We note the extremely detailed and explicit summaries. We note that there remain a few clinical indications for DES but the cost-effectiveness evidence appears strong and convincing.*	Comment noted. DESs are recommended in circumstances outlined in FAD section 1.1.
NHSQIS Reviewer 2		Whether you consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS. *The science appears sounds*	Comment noted.
NHSQIS Reviewer 2		Whether you consider that there are any potential policy implications for SEHD? *There are policy implications from the provisional recommendations and these*	DESs are recommended in circumstances outlined

		will be explored now with colleagues and with the publication of the FAD.	in FAD section 1.1.
NHS Supply Chain		NHS Supply Chain, established on 1 October 2006, is a 10 year contract operated by DHL Logistics, on behalf of the NHS Business Services Authority. NHS Supply Chain manages the procurement and delivery of more than 500,000 products for NHS trusts across 11 product categories, including national procurement responsibility for cardiology consumables. NHS Supply Chain was set up as part of the Department of Health's Supply Chain Excellence Programme, which promoted a new commercial landscape across the NHS. The Department believes that partnering with DHL - a specialist supply chain provider - is in the best interests of the NHS, patients and the taxpayer. NHS Supply Chain's overriding aim is to deliver more than £1 billion in savings to the NHS over the 10 year contract term, through the provision of cost-effective supply chain services to health providers across England. These savings will be redirected back to NHS managers for patient care services.	Comments noted.
NHS Supply Chain		Under section 4 (sub section 4.3.13) Evidence and Interpretation of the appraisal document, NICE acknowledge that there is no national procurement of DESs at a price premium that would fall below £300. NHS Supply Chain's status places us in the ideal position to potentially establish a national procurement solution for the NHS for drug eluting stents and bare metal stents with a price differential less than £300. If NHS Supply Chain were to undertake a tender exercise to establish a national agreement for bare metal and drug eluting stents, it's resultant	Comments noted. The Institute has received data from PASA for 2007/08. See FAD section 3.6.

		success would be dependent on the suppliers willingness to co-operate and work with a national procurement body. Any tender submissions would need to reflect the current prices paid by NHS trusts for these products on an individual basis. It would not be of benefit to the NHS to establish an agreement that addresses the price differential but penalises individual trusts by forcing them to pay higher prices for products than they currently pay. Any tender exercise would also need engagement and support from the clinical community. Establishing a national agreement at the appropriate rates with a price differential below £300 will allow the NHS continued access to this product at cost effective rates.	
Comments on spreadsheet accompanying addendum 6			
Abbott Laboratories Ltd		Thank you for the opportunity to comment on the Economic Model. Abbott acknowledges and supports all the statements and objections made in the British Cardiac Industry Association (BCIA) submission.	Comments noted.
Abbott Laboratories Ltd		**Model Structure** The model is decision tree based, using probabilities of events (i.e. revascularisation) to determine the overall expected outcomes. In this analysis Drug Eluting Stents, DES, were compared against Bare Metal Stents, BMS, over a 1 year time horizon. Since the spreadsheet is non-executable, this restricts our ability to explore the formulae and cell-linkage in the model to asses for calculation errors. We are also unable to comment on the consistency of the model with the Technology Appraisal Report, TAR.	Comments noted. See section 4.4.1.9 of the technology appraisal process guide with regard to read-only versions of the model.

Abbott Laboratories Ltd		**Time Horizon** There is a restricted time horizon and Abbott believes this should be modelled to 2 years in order to fully assess the cost effectiveness of DES versus BMS. This is particularly important given that repeat revascularisations accrue beyond year 1 and the AMI utility gain will also persist into each subsequent year.	The Appraisal Committee considered a one year time horizon to be appropriate see FAD section 4.3.6.
Abbott Laboratories Ltd		**Budget Impact** By only considering DES compared against BMS the assessment does not take into account the budget impact from those patients who physicians would refer to surgery because the clinical outcome from stenting with BMS would be unsatisfactory.	DESs are recommended in circumstances outlined in FAD section 1.1.
Abbott Laboratories Ltd		**Clinical Data Inputs** **2.1 Acute Coronary Syndromes** In the assessment model the data input for Acute Coronary Syndromes, ACS, and therefore those patients who would receive dual anti-platelet therapy for 12 months regardless of stent type was 44%. Recently presented data (Ludman 2007) on the BCIS audit returns for year ending 2006 shows this has risen to 48.5%, we request that the most up to date figures should be employed in the model.	See addendum 7 and FAD sections 4.2.22, 4.3.10 and 4.3.13.
Abbott Laboratories Ltd		**Absolute and Relative Risk Reduction** The main driver of effectiveness is the absolute and percentage risk reduction in the need for revascularisation procedures. Abbott considers this is a suitable measure of effectiveness provided the inputs are based on clearly referenced multi-centre audited data.	Comments noted.
Abbott Laboratories		**Absolute Risk** For Absolute Risk the model uses 10% for elective patients and 13% for non-	The Appraisal Committee did not accept all the

Ltd		elective, but it is unclear how these figures have been derived. Abbott recommends using the data below from a multi-centre audited database, rather than a single centre source: BMS Absolute Revascularisation Risk of 13% is taken from the Scottish registry prior to DES (year 2000-2001, Pell & Slack 2004). In addition if the data takes into consideration the relative number of patients with ACS, 48.5% for 2006, the Absolute Revascularisation Risk for the unselected population is 14.7%.	parameters and assumptions in LRiGs model see FAD sections 4.3.4, 4.3.6, 4.3.12, 4.3.13 and 4.3.14. The Appraisal Committee considered BCIS's assumptions see FAD sections 4.2.23, 4.2.28, 4.3.13 and 4.3.14.
Abbott Laboratories Ltd		**Relative Risk** For Relative Risk the model presents 2 scenarios 55% and 65%, Abbott believes that 65% is more representative of the Randomised Controlled Trial, RCT, data. It is of note that in the assessment model diabetics have an unusually low relative risk based on the CTC database. This is because non-elective diabetic patients are portrayed to have a relative risk of 0.9, which is combined with 1.38 for elective patients. It would be perverse for a known risk factor, repeatedly identified in Randomised Clinical Trials to have a Relative Risk of less than 1 in non-elective patients. Abbott recommends using the data below previously submitted by clinical experts from BCIS and derived from RCT rather single centre data: Relative Risk for the following independent risk factors: Small Vessels 1.75, Long Lesions 1.35, Diabetes 1.52. This would lead to a Risk Reduction gain from DES of: 69% Small Vessels, 70% Long Lesions, 61% Diabetes.	The Appraisal Committee was aware of the views expressed by consultees and commentators about the CTC database. Therefore it did not accept all the parameters and assumptions in LRiGs model see FAD sections 4.3.4, 4.3.7, 4.3.12, 4.3.13 and 4.3.14. The Appraisal Committee considered BCIS's assumptions see FAD sections 4.2.23, 4.2.28, 4.3.13 and 4.3.14.

<table>
<tr>
<td>Abbott Laboratories Ltd</td>
<td></td>
<td>Number of Stents
There appears to be a discrepancy in the Assessment Model on the number of stents per procedure used in the combined Table A of Addendum 6 and that displayed in the separate elective and non-elective datasets of Addendum 5. Abbott seeks clarification of the correct value.</td>
<td>See addendum 7 section 2.1.3 for clarification of this point.</td>
</tr>
<tr>
<td>Abbott Laboratories Ltd</td>
<td></td>
<td>Re-treatment for Revascularisation

In the model the following data is used for re-treatment, however it is unclear what the source is for this data.
<table>
<tr><th></th><th>Elective</th><th>Non-Elective</th></tr>
<tr><td>Proportion as unstented PCI</td><td>36.60%</td><td>27.40%</td></tr>
<tr><td>Proportion as stented PCI</td><td>54.50%</td><td>54.70%</td></tr>
<tr><td>Proportion as CABG</td><td>9.00%</td><td>17.90%</td></tr>
</table>
Abbott has concerns over the high percentage of unstented PCI employed in the model, which is double the rate we would expect. In the meta-analysis of SPIRIT II and III, only 14% of Target Lesion Revascularisations were retreated with balloon angioplasty alone.
Abbott is also concerned that there is no transparency on whether the stent, and therefore the costs associated, for the stented PCI is in fact DES or BMS. We seek clarification on what percentage of the stented PCI patients received DES and what percentage BMS.</td>
<td>Comments noted.
Table 8-7 in the assessment report states that the source is the Liverpool CTC audit data.

The model assumes that all repeat interventions with stented PCI use DESs.</td>
</tr>
<tr>
<td>Abbott Laboratories Ltd</td>
<td></td>
<td><u>Cost Data Inputs</u>
The cost of DES is offset against the cost savings associated with fewer revascularisation procedures (e.g. reduced number of PCI, CABG, outpatient visits, etc.) It is therefore critical for the Appraisal Committee to ensure the assessment model is run with accurate up to date cost data.</td>
<td>DESs are recommended in circumstances outlined in FAD section 1.1.</td>
</tr>
</table>

<table>
<tr>
<td>Abbott Laboratories Ltd</td>
<td></td>
<td>Reference Costs
The model uses reference costs from 2003-04, which have now been superseded by the 2005-06 data. Abbott would recommend these new costs are used as the default in the model.
<table>
<tr><th>Item</th><th>2003-04 Reference Cost</th><th>2005-06 Reference Cost</th></tr>
<tr><td>Cardiology 1st out-patient attendance</td><td>£134</td><td>£148</td></tr>
<tr><td>Cardiac surgery 1st out-patient attendance</td><td>£208</td><td>£274</td></tr>
<tr><td>Cardiology out-patient follow up</td><td>£94</td><td>£104</td></tr>
<tr><td>Cardiac surgery out-patient follow up</td><td>£156</td><td>£182</td></tr>
<tr><td>Angiography</td><td>£724</td><td>£838</td></tr>
<tr><td>PCI (elective)</td><td>£2609</td><td>£3093</td></tr>
<tr><td>Unstented PCI</td><td>£1453</td><td>£1937</td></tr>
<tr><td>CABG (elective)</td><td>£7066</td><td>£8172</td></tr>
</table>
</td>
<td>The Appraisal Committees considerations of this point are described in FAD section 4.2.22, see also addendum 7.</td>
</tr>
<tr>
<td>Abbott Laboratories Ltd</td>
<td></td>
<td>Price Delta DES and BMS
In addition Abbott assesses the relative premium of a DES over a BMS in 2007 to be £300, not the £600 considered in the model. Abbott would recommend that in view of the length of time this assessment has taken that a new independent price survey is conducted.</td>
<td>The Institute has received data from PASA for 2007/08; see FAD section 3.6.</td>
</tr>
<tr>
<td>Abbott Laboratories Ltd</td>
<td></td>
<td>QALY Loss Awaiting Repeat Revascularisation
For QALY loss awaiting repeat revascularisation the assessment model employs NHS wait time statistics for Quarter 4 2004-05, PCI 16 weeks and</td>
<td>The Appraisal Committees considerations of this point are described in FAD</td>
</tr>
</table>

		CABG 9 weeks with 4 week wait prior to joining the list. Again due to the length of time this appraisal has taken these are out of date. Abbott would recommend the methodology from the attached BCIA report based on the Hawkins formulae. This consists of 3 elements: 6 week wait to first out-patient attendance (waiting time statistics Q4 2006) 11.1 week wait for angiography (HES 2005-06) 8 week wait PCI and 9.3 week wait CABG (HES 2005-06)	section 4.2.22, see also addendum 7.
Abbott Laboratories Ltd		**Cost Effectiveness** **4.1 Weighted Distribution of Risk Factors** The authors appear to have calculated the 'weighted' distribution of patients with each permutation of the risk factors based on the assumption that the respective likelihoods of experiencing each of the risk factors are independent of one another. In reality, it is possible that the existence of one risk factor is also lined with the probability of experiencing one or more others. This would imply that the probability of a patient experiencing all three (i.e. the highest risk) group are underrepresented in the analysis. As such, the weighted results are likely to underestimate the true cost-effectiveness of DES.	Comments noted.
Abbott Laboratories Ltd		Summary Abbott believes it would be unsound to issue guidance based on the current assessment model without making the following changes: The model should be based on a 2 year time horizon. The data inputs should be changed to reflect that 48.5% of UK patients are non-elective. The Absolute Risk of revascularisation should be input at 14.7%, based on the Scottish Registry and adjustment for the 2006, 48.5%, ACS rate. The Relative Risk should take into account the following independent risk factors: Small Vessels 1.75, Long Lesions 1.35, Diabetes 1.52. This would lead to a Risk Reduction gain from DES of: 69% Small Vessels, 70% Long Lesions, 61% Diabetes.	Comments noted. See responses to Abbott Laboratories' specific comments above.

		The number of stents used in the combined data sets for Addendum 5 and 6 are clarified and applied consistently in the model. The Re-treatment of Revascularisations should be adjusted to reflect a 14% re-treatment with balloon only PCI and clarification of what percentage of stented PCI includes DES. The procedural costs should be taken from the NHS reference costs 2005-06. A new independent survey should be conducted to determine the price delta between DES and BMS to ensure that costs are representative of 2007. The QALY Loss Awaiting Repeat Revascularisation is rerun using the Hawkins formulae consisting of the following three elements: 6 week wait to first out-patient attendance (waiting time statistics Q4 2006) 11.1 week wait for angiography (HES 2005-06) 8 week wait PCI and 9.3 week wait CABG (HES 2005-06). Correct the 'weighted' distribution of patients with multiple risk factors. The Appraisal Committee should consider the budget, logistical and social impact of restricting DES usage, which would increase the rate of Coronary Artery Bypass Surgery, and remove patient choice for a less invasive procedure.	
British Cardiovascular Industry Association		1. **Introduction** 1.1. Whilst the structure of the economic model seems to include for the major costs and effects in the first year, the model is somewhat simplistic and limited in its capacity to fully explore the cost effectiveness of DES. 1.2. We have major concerns over many of the data inputs, which are either out of date, use single centre data where a wider literature exists or are inconsistent with previous Assessment report addenda. The multiple and serious limitations of the model lead BCIA to continue to recommend that this Appraisal be referred to	Comments noted. The Appraisal Committee did not accept all the parameters and assumptions in LRiGs model see FAD sections 4.3.4, 4.3.5, 4.3.6, 4.3.7, 4.3.10, 4.3.11, 4.3.12, 4.3.13 and 4.3.14.

		the Decision Support Unit.	
British Cardiovascular Industry Association		2. **Modelling methods** 2.1. Some of the inputs are hard coded rather than being transparently derived from raw data. This specifically applies to the QALY loss awaiting PCI/CABG, the AMI utility gain and the AMI costs saving. 2.2. The model does not attempt to handle parameter uncertainty using probabilistic sensitivity analysis and therefore LRiG's have not followed NICE's Guide to the Methods of Technology Appraisal. This is a serious limitation. It is possible to estimate confidence limits around many of the data inputs, so we see no reason why LRiG should not have followed this practice. 2.3. The model does not explore longer-term costs effectiveness beyond the first year, probably due to LRiG's view that there are few data points beyond one year. This is certainly not the case now and given the potential impact of the draft guidance, it would be both diligent and fair to explore the longer-term. This is particularly important given that repeat revascularisations accrue beyond year 1 and the AMI utility gain will also persist into each subsequent year.	Comments noted. The Appraisal Committee considered a one year time horizon to be appropriate see FAD section 4.3.6.
British Cardiovascular Industry Association		3. **DES Price Premium** 3.1. The economic model investigates DES cost effectiveness at various levels of price premium. Interpretation of the results is critically dependent upon the price premium that the Appraisal Committee decides is representative of the UK. BCIA will not engage in specific discussion of prices due to issues around anti-	Comments noted. The Institute has received data from PASA. See FAD section 3.6.

		trust and competition law. We simply request, for transparency and methodological reasons, clarification of how the correct DES price premium will be identified. If an average BMS price is used, as appears to be the case, an average DES price should also be used. Averages would also be consistent with the use of NHS reference costs elsewhere in the model as these are also averages.	
British Cardiovascular Industry Association		4. **New UK Data on Proportion of Patients with Acute Coronary Syndromes (ACS)** 4.1. Recently presented BCIS data for 2006 shows that the proportion of patients presenting with ACS (i.e. incurring non-elective costs and resource use) has risen to 48.5% (Ludman 2007). This means that the proportions used in combining LRiG's elective and non-elective datasets, and the proportion of DES patients who require 9-months additional clopidogrel should be revised. The impact of this on individual data inputs is given below.	The Appraisal Committees considerations of this point are described in FAD sections 4.3.10 and 4.3.13; see also addendum 7 and FAD section 4.2.22.
British Cardiovascular Industry Association		5. **The Absolute Risk of Repeat Revascularisation with BMS** 5.1. It is not clear how the absolute risk of repeat revascularisation with BMS have been chosen to be 10% for elective patients and 13% for non-elective patients. The submission to NICE by NHS QIS (dated 13th January 2006) states: *"The Scottish Coronary Revascularisation Register Report for 2003-04 reports a repeat revascularisation rate at 12 months of 12.9% (95%CI 12.1-13.7; n=6525 vs 7.79% in Liverpool) for patients undergoing elective PCI and 16.6% (15.7-17.6; n=5921 vs 10.15% in Liverpool) for patients undergoing PCI for unstable*	The Appraisal Committee did not accept all the parameters and assumptions in LRiGs model see FAD sections 4.3.4, 4.3.6, 4.3.12, 4.3.13 and 4.3.14. The Appraisal Committee considered BCIS's assumptions see FAD

		coronary syndromes." 5.2. Combining these data in the correct proportions of acute coronary syndrome (ACS) and non-ACS patients (48.5% ACS, Ludman 2007), the absolute risk of repeat revascularisation for the combined, unselected population is **14.7%**. The model should be re-run using these Scottish registry data.	sections 4.2.23, 4.2.28, 4.3.13 and 4.3.14.
British Cardiovascular Industry Association		6. **The Risk Reduction Associated with DES** 6.1. The model presents alternatives of 55% and 65% risk reduction associated with DES. A 65% risk reduction is more representative of the randomised trials and the use of trial-based treatment effects is consistent with NICE's Guide to the Methods of Technology Appraisals. The model should be re-run using the risk reductions previously submitted by the British Cardiovascular Intervention (BCIS) Society (unselected population 0.60, long lesions 0.69, small vessels 0.70, diabetes 0.61).	The Appraisal Committee did not accept all the parameters and assumptions in LRiGs model see FAD sections 4.3.4, 4.3.7, 4.3.12, 4.3.13 and 4.3.14. The Appraisal Committee considered BCIS's assumptions see FAD sections 4.2.23, 4.2.28, 4.3.13 and 4.3.14.
British Cardiovascular Industry Association		7. **Relative Risks for the Independent Risk Factors** 7.1. The model employs an unusually low relative risk (RR) for diabetes (1.19) which results from the sole reliance on the CTC database and a combination of relative risks of 0.90 for non-elective patients and 1.38 for elective patients. The non-elective RR appears to be a spurious result because a RR of <1 for a risk	The Appraisal Committee was aware of the views expressed by consultees and commentators about the CTC database. Therefore it did not accept

<table>
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<td>factor that has repeatedly been shown to increase the relative risk does not make sense.

7.2. It would be more reasonable the use the relative risks for the individual risk factors previously submitted by BCIS as they are derived from the wider literature and are not solely reliant upon the CTC database.</td>
<td>all the parameters and assumptions in LRiGs model see FAD sections 4.3.4, 4.3.7, 4.3.12, 4.3.13 and 4.3.14.

The Appraisal Committee considered BCIS's assumptions see FAD sections 4.2.23, 4.2.28, 4.3.13 and 4.3.14.</td>
</tr>
<tr>
<td>British Cardiovascular Industry Association</td>
<td></td>
<td>8. <u>NHS Reference Costs</u>
8.1. The model uses reference costs from 2003-04. These are out of date, as the Department of Health has now published costs for 2005-06. Table 1 compares the costs used in the model with the most recent reference costs. 2003-04 reference costs under-estimate the costs associated with repeat revascularisation and thus render the current model inaccurate. The model should be re-run using 2005-06 reference costs.

<table>
<tr><th>Item</th><th>2003-04 Reference Cost</th><th>2005-06 Reference Cost</th><th>Difference</th></tr>
<tr><td>Cardiology 1st out-patient attendance</td><td>£134</td><td>£148 (code 320F)</td><td>+£14</td></tr>
<tr><td>Cardiac surgery 1st out-patient</td><td>£208</td><td>£274 (code</td><td>+£66</td></tr>
</table>
</td>
<td>The Appraisal Committees considerations of this point are described in FAD section 4.2.22, see also addendum 7.</td>
</tr>
</table>

		attendance		172F)	
		Cardiology out-patient follow up	£94	£104 (code 320F)	+£10
		Cardiac surgery out-patient follow up	£156	£182 (code 172F)	+£26
		Angiography	£724	£838 (day case E14)	+£114
		PCI (elective)	£2609	£3093	+£484
		Unstented PCI	£1453	£1937	+£484
		CABG (elective)	£7066	£8172	+£1106
		Table 1. Comparison of 2003-04 reference costs used in the LRiG model and the latest 2005-06 reference costs.			
British Cardiovascular Industry Association		9. **<u>Calculation of QALY Loss Awaiting Repeat Revascularisation.</u>** 9.1. LRiG use a 16 week wait for PCI, 9 week wait for CABG and assume a 4 week wait prior to joining the list in order to calculate the QALY loss awaiting repeat revascularisation, derived from NHS waiting time statistics for quarter 4 2004-05. These data are again out of date, as the Department of Health has published waiting time statistics up to the 4th quarter 2006 and HES data for 2005-06. 9.2. The waiting time for PCI and CABG procedures should be taken from HES data, as this is specific to revascularisation, rather than, for example the entry for 'cardiothoracic surgery' in the NHS waiting time statistics, as cardiothoracic surgery includes other, non-revascularisation procedures.			This point is clarified in FAD section 4.2.22 and in addendum 7.

		9.3. LRiG's formula for estimating total waiting times is somewhat imprecise compared with that published by Hawkins et al (2005), who considered the total wait to be made up of three elements: time waiting for first consultant appointment, time waiting for coronary angiography and time waiting for the revascularisation procedure. Latest data from the Dept. of Health suggests that these inputs should be as follows: 6 weeks for 1st cardiology/cardiac surgery out-patient attendance (waiting time statistics, Q4 2006), 11.1 weeks waiting for angiography (HES 2005-06), 8.0 weeks waiting for PCI procedure and 9.3 weeks waiting for CABG procedure (HES 2005-06). The model should be re-run using the Hawkins formula and the data given above.	
British Cardiovascular Industry Association		10. **Combination of Elective and Non-elective Datasets** 10.1. The combination of the incremental costs and utilities from the separate elective and non-elective models should be according to national proportion of 48.5% non-elective, rather than the single centre, CTC proportion. 10.2. LRiG should also explain the discrepancy between the number of stents per procedure in their combined Table A of Addendum 6' and the number of stents used shown in the separate elective and non-elective datasets in Table A of Addendum 5'. It is our belief that Table A of Addendum 6' is incorrect and the number of stents per procedure is particularly inaccurate for small vessels and long lesions + small vessels. However, if Table A of Addendum 6' is correct and the individual elective and non-elective number of stents per procedure is wrong, then the model overestimates the ICERs for small vessels and long lesions + small vessels in particular. These key inputs should be checked and the correct	The Appraisal Committees considerations of this point are described in FAD sections 4.3.5 and 4.3.13; see FAD sections 4.2.23 and addendum 7 for clarification.

		data should be entered into the model.	
British Cardiovascular Industry Association		11. **<u>Acute Coronary Syndromes</u>** 11.1. NICE's announcement of the development of a clinical guideline for the management of patients with ACS and the stated relevance of the guidance on the use of coronary stents to that guideline, suggests that ACS should be considered as an additional sub-group within this Review. 11.2. There are additional clinical and economic grounds for doing so in that the 16.6% repeat revascularisation rate for patients with ACS shown in the Scottish registry gives cause to believe that there may be substantial benefit from DES in this population. Secondly, ACS patients receiving DES do not require 9m additional Clopidogrel for reasons previously stated and accepted by the Appraisal Committee. This takes out a major cost item and is likely to have a major impact on the ICER for ACS patients. 11.3. BCIA have previously shown that ACS and unstable angina do occur in the literature as independent risk factors for repeat revascularisation (BCIA response to Assessment Report Addendum), and that the risk for unstable angina is of a similar order to that for long lesions (odds ratio ~ 1.40). One study (Gotschall et al 2006) reported an odds ratio for target vessel revascularisation of 3.23 for ACS. 11.4. We propose that ACS be added as an additional sub-group for consideration, with modelling based on non-elective reference costs and resource use as these patients present in the non-	The Appraisal Committees considerations of this point are described in FAD section 4.3.10 and 4.3.13; see also addendum 7 and FAD section 4.2.22.

		elective setting.	
British Cardiovascular Industry Association		12. **Summary** 12.1. The model should be re-run incorporating: 12.1.1. A clear and transparent determination of the average DES price premium. 12.1.2. Data inputs revised based on a proportion of 48.5% non-elective patients. 12.1.3. 14.7% repeat revascularisation rate from the Scottish registry. 12.1.4. The trial-based absolute risk reductions previously submitted by BCIS. 12.1.5. The relative risks for the individual risk factors identified by BCIS. 12.1.6. The latest NHS reference costs (2005-06). 12.1.7. QALY loss based on the latest NHS waiting times and the Hawkins method. 12.1.8. Clarification of the correct number of stents per procedure, especially for small vessels and small vessels + long lesions. 12.1.9. ACS as a separate risk factor group. 12.2. This consultation on the economic model is welcome and has	The Appraisal Committees considerations of this point are described in FAD sections 4.3.10, 4.3.12, 4.3.13 and 4.3.14; see also addendum 7 and FAD sections 4.2.22, 4.2.23, 4.2.27 and 4.2.28.

		revealed more limitations than was previously appreciated. The outcome of the Review would be perverse if it were based on such out of date, unreliable and questionable inputs and the Institute should take urgent steps to make sure these issues are addressed.	
British Cardiovascular Intervention Society		The model is a basic health economic model that depends for its value on the accuracy of the figures imputed into it. The model as such is exquisitively sensitive to some key parameters. The decision regarding cost efficacy appears thus to be dependant on the choice of the various absolute values used – why certain values were chosen and used in this model continues to remain unclear. We continue to be perplexed as to why the values used are different from those from published data or indicated as valid by the N.I.C.E committee Yet again we wish to bring to the attention of the N.I.C.E executive the falure by the N.I.C.E committee to use apprpropriate and accurate data in deriving the Guidance on DES	Comments noted. See responses to specific comments below.
British Cardiovascular Intervention Society		**. Absolute Risk of Repeat Revascularisation** • It is unclear why the absolute risks of repeat revascularisation with BMS have been set at 10% for elective patients and 13% for non-elective patients, averaging to 11% for all patients. This is inconsistent with the Appraisal Committee's previous request that LRiG update the economic model with absolute risk of repeat revascularisation taken from the Scottish registry (Addendum 3' page 48). The submission to NICE by NHS QIS (dated 13th January 2006) states: "*The Scottish Coronary Revascularisation Register Report for 2003-04*	The Appraisal Committee did not accept all the parameters and assumptions in LRiGs model see FAD sections 4.3.4, 4.3.6, 4.3.12, 4.3.13 and 4.3.14. The Appraisal Committee considered BCIS's

		*reports a repeat revascularisation rate at 12 months of **12.9%** (95%CI 12.1-13.7; n=6525 vs 7.79% in Liverpool) for patients undergoing elective PCI and **16.6%** (15.7-17.6; n=5921 vs 10.15% in Liverpool) for patients undergoing PCI for unstable coronary syndromes.*" It is clearly perverse to request that specific data be used in the economic model and to then ignore those data. If one combines the Scottish data submitted by NHS QIS (above) using the correct national proportion of ACS patients (44%), then the overall unselected population absolute risk of repeat revascularisation is **14.5%**. • BCIS has always argued that a value of 13% for absolute risk is justified from the randomised trials and registries in the worldwide literature, However if we were to follow the NICE recommendation of Jan 2006 **14.5%** would be the correct starting point in the economic model for the unselected population. We would continue to support and be happy to justify (as we have done previously) the 13% figure despite this , since we believe this is a true reflection of the current clinical scenario. • There is **no** justification on any grounds (scientific, evidence based, or clinically reported) to reduce the base rate with BMS to less than 13%	assumptions see FAD sections 4.2.23, 4.2.28, 4.3.13 and 4.3.14.
British Cardiovascular Intervention Society		**2. Relative Risks for the Independent Risk Factors** • It is unclear why the relative risks for the independent risk factors remain solely based on the CTC database when BCIS have previously presented all relevant data and repeatedly from the literature. Whilst the CTC relative risks for small vessels and long lesions are within the literature range, the relative risk for diabetes is outside the lower range	The Appraisal Committee was aware of the views expressed by consultees and commentators about the CTC database. Therefore it did not accept

		(CTC 1.19, Addendum 6', literature mean 1.52, range 1.34-1.18). LRiG's low value is driven by the use of a relative risk of 0.90 for non-elective patients and is clearly a spurious result for this positively-predictive factor. Further it is clear form the CTC database that the population is a low risk one with wa low incidence od diabetes. • The economic models accuracy and robustness would be improved significantly if BCIS's previously submitted relative risks (shown below in Table 1) were used when evaluating the excess risk associated with long lesions, small vessels and diabetes. • These values are not derived from "BCIS" They come from peer reviewed published data and contain angiographically driven but more importantly non angiographically driven RCT and registries including the N.I.C.E –favoured BASKET study.	all the parameters and assumptions in LRiGs model see FAD sections 4.3.4, 4.3.7, 4.3.12, 4.3.13 and 4.3.14. The Appraisal Committee considered BCIS's assumptions see FAD sections 4.2.23, 4.2.28, 4.3.13 and 4.3.14.

Sub-group	Relative Risk	Comment	Source
Small vessels			
	1.55	12m non-MI related TVR, stents <3mm diameter	BASKET trial, Kaiser et al 2006
	1.17	12m TLR, vessels <2.75mm vs vessels >2.75mm	SIRIUS trial, Holmes et al 2004
	2.09	24m TLR, minimum lumen diameter <3mm	Stent design trial, Elbaz et al 2002
	1.79	9m revascularisation, vessels <2.75mm vs >2.75mm in lesions <20mm length (estimate)	Clinical database, Ellis et al 2004
	1.52	12m reintervention, vessels <2mm, elective patients	Assessment Report Addendum 3''
	2.62	12m reintervention, vessels <2mm, non-elective patients	Assessment Report Addendum 3''
	1.78	12m TVR, vessels <3mm vs vessels >3mm (estimate)	Clinical database, Gotschall et al 2006
	1.33	12m TLR (estimate)	Clinical database, Kornowski et al 1999
	1.71	6m TLR, mimimum lumen diameter <3mm	Clinical database, Kastrati et al1997
	1.84	9m TLR, <3mm vs vessels >3mm (estimate)	ENDEAVOR II trial, Fajadet et al 2006
	1.85	12m TLR, longer stent length	TAXUS IV trial, Stone et al 2004
Mean	***1.75***		
Long lesions			
	1.10	12m TLR (estimate) per 5mm lesion length increase, no angiographic follow up	Trial meta analysis, Cutlip et al 2002
	1.18	12m TLR, lesions >13.5mm vs lesions < 13.5mm	SIRIUS trial, Holmes et al 2004
	1.02	12m TVR, per unit (undefined) increase	Clinical database, Agema et al 2003
	2.11	9m revascularisation, lesions >20mm vs <20mm in vessels >3.25mm diameter (estimate)	Clinical database, Ellis et al 2004
	1.01	12m revascularisation, per 1mm increase in stent length	Clinical database, Wu et al 2004
	1.20	12m reintervention, lesions >20mm, elective patients	Assessment Report Addendum 3''
	1.19	12m reintervention, lesions >20mm, non-elective patients	Assessment Report Addendum 3''
	2.15	12m TVR, lesions >20mm vs lesions <20mm (estimate)	Clinical database, Gotschall et al 2006
	1.42	12m TVR, lesions >20mm vs lesions <20mm (estimate)	PRESTO trial, Singh et al 2005
	1.41	9m TLR, lesions >16mm vs lesions <16mm (estimate)	ENDEAVOR II trial, Fajadet et al 2006
	1.04	12m TLR, longer stent length	TAXUS IV trial, Stone et al 2004
Mean	***1.35***		
Diabetes			
	1.81	12m TVR	RESEARCH registry, Lemos et al 2004
	1.51	12m TLR	SIRIUS trial, Holmes et al 2004
	1.80	12m TVR	TAXUS IV trial, Pinto et al 2006
	1.42	12m TLR (estimate), no angiographic follow up	Meta analysis, Cutlip et al 2002
	1.57	12m TVR	Clinical database, Agema et al 2003
	1.52	12m revascularisation by CABG	Clinical database, Wu et al 2004
	1.38	12m reintervention, elective patients	Assessment Report Addendum 3''
	1.36	12m TVR (estimate)	Clinical database, Gotschall et al 2006
	1.35	12m TLR (estimate)	Clinical database, Kornowski et al 1999
	1.34	6m TLR (estimate)	Clinical database, Kastrati et al1997
	1.73	12m TLR (estimate)	Clinical database, Jilaihawi et al 2005
	1.39	9m TLR	ENDEAVOR II trial, Fajadet et al 2006
Mean	***1.52***		

Table 1. Relative risk for repeat revascularisation for the independent risk factors of small vessels, long lesions and diabetes.

Using these appropriate relative risk adjustments will result in the following values for TVR needing to be inserted in the model for these higher risk

		patients: Small Vessels: 1.75 x 13% = 23% Long Lesions: 1.35 x 13% = 18% Diabetes: 1.52 x 13% = 20% Of course if we started with a 14.5% absolute risk as suggested by NICE then these figures would be higher still.	
British Cardiovascular Intervention Society		**) Relative Risk Reduction for DES** • The 55% risk reduction used in one of the model scenarios is an under-estimate of the true 60-70% reduction shown by the randomised trials. The model scenario that employs a 65% risk reduction is more representative of the randomised trials, but the model would be more reliable if the literature-based risk reductions previously presented by BCIS were used in the model (reproduced in Table 2). Again these are a large set of data from peer review publication including both angiographically driven and non angiographically driven outcomes.	The Appraisal Committee did not accept all the parameters and assumptions in LRiGs model see FAD sections 4.3.4, 4.3.7, 4.3.12, 4.3.13 and 4.3.14. The Appraisal Committee considered BCIS's assumptions see FAD sections 4.2.23, 4.2.28, 4.3.13 and 4.3.14.

Sub-group	DES Risk Reduction	Comment	Source
Base case			
	0.67	12m TVR	RESEARCH registry, Lemos et al 2004
	0.75	12m TLR	SIRIUS trial, Holmes et al 2004
	0.65	12m TVR, no angiographic follow up	TAXUS IV trial, Pinto et al 2006
	0.53	9m TVR	TAXUS VI trial, Dawkins et al 2005
	0.56	9m TLR, no angiogram subset	ENDEAVOR II trial, Fajadet et al 2006
	0.41	12m non-MI related TVR (estimate)	BASKET trial, Kaiser et al 2006
Mean	***0.60***		
Small vessels			
	0.67	12m TVR, vessels </= 2.5mm	RESEARCH registry, Lemos et al 2004
	0.76	12m TLR, vessels 2.5-3.0mm in non-diabetics	SIRIUS trial, Holmes et al 2004
	0.83	9m TLR, vessels <2.5mm	TAXUS VI trial, Dawkins et al 2005
	0.61	12m non-MI related TVR, stents <3mm	BASKET trial, Kaiser et al 2006
	0.57	9m TLR, vessels <2.5mm	ENDEAVOR II trial, Fajadet et al 2006
	0.71	12m TLR, vessels <3mm (estimate)	TAXIS IV trial, Stone et al 2004
Mean	***0.69***		
Long lesions			
	0.59	12m TVR, lesion >/= 33mm	RESEARCH registry, Lemos et al 2004
	0.78	12m TLR, lesions >15mm in non-diabetics with vessels >3mm	SIRIUS trial, Holmes et al 2004
	0.83	9m TLR, lesions >26mm	TAXUS VI trial, Dawkins et al 2005
	0.57	9m TLR, lesions >16mm	ENDEAVOR II trial, Fajadet et al 2006
	0.75	12m TLR, lesions > 20mm	TAXIS IV trial, Stone et al 2004
Mean	***0.70***		
Diabetes			
	0.28	12m TVR	RESEARCH registry, Lemos et al 2004
	0.77	12m TLR, in vessels >3mm, lesions 12-15mm in length	SIRIUS trial, Holmes et al 2004
	0.88	9m TLR	TAXUS VI trial, Dawkins et al 2005
	0.51	9m TLR	ENDEAVOR II trial, Fajadet et al 2006
	0.63	12m TLR	TAXIS IV trial, Stone et al 2004
Mean	***0.61***		

Table 2. Relative risk gained from DES for the independent risk factors of small vessels, long lesions and diabetes.

British Cardiovascular

Drug Eluting Stent Price Premium

- The model investigates the cost effectiveness of DES across a range of

The Institute has received data from PASA for

<table>
<tr>
<td>Intervention Society</td>
<td></td>
<td>price premium. A key decision for the Appraisal Committee will be what premium is realistic. Comments from BCIS members leads us to conclude that £300 is a realistic premium and most appropriate to use in the model. This is consistent with previous evidence presented to the committee and within the range previously publically acknowledged by the Committee.</td>
<td>2007/08; see FAD section 3.6.</td>
</tr>
<tr>
<td>British Cardiovascular Intervention Society</td>
<td></td>
<td>
NHS Reference Costs

• The reference costs used in the model date from 2003-04 and are not representative of costs for 2008 onwards when the new guidance will apply. Table 3 shows the latest and most up to date NHS reference costs for 2005-06. As these are higher, the 2003-04 costs currently used in the model work to the disadvantage of DES cost efficacy. The model we believe reflect true cost efficacy and therefore must be re-run using the most bcontemporary 2005-06 reference costs.
<table>
<tr><th>Cost Item</th><th>Current Model Input (2003-04 Costs)</th><th>2005-06 Reference Cost</th></tr>
<tr><td>Cardiology out-patient visit</td><td>£134</td><td>£148 (code 320F)</td></tr>
<tr><td>Cardiac surgery out-patient visit</td><td>£208</td><td>£274 (code 172F)</td></tr>
<tr><td>Angiography</td><td>£724</td><td>£838 (day case E14)</td></tr>
<tr><td>Unstented PCI</td><td>£1453.40</td><td>£1937.40</td></tr>
<tr><td>CABG</td><td>£7066</td><td>£8172</td></tr>
<tr><td>Cardiology out-patient f/up visit</td><td>£94</td><td>£104 (code 320F)</td></tr>
</table>
</td>
<td>These points are clarified in addendum 7 and FAD section 4.2.22.</td>
</tr>
</table>

Cardiac surgery out-patient f/up visit	£156	£182 (code 172F)	

Table 3. Revised cost inputs based on 2005-06 reference costs.

British Cardiovascular Intervention Society

Waiting Times for PCI and CABG

- In order to calculate QALY loss awaiting repeat revascularisation, the model employs a 16 week wait for PCI, a 9 week wait for CABG and assumes a 4 week wait prior to joining the list. A methodology that more realistically reflects real-world UK practice was reported by Hawkins, Sculpher and Rothman (2005), who considered the total wait to be made up of three elements: time waiting for first consultant appointment, time waiting for coronary angiography and time waiting for the revascularisation procedure.

- Table 4 shows the latest available NHS data inputs to this calculation. The current LRiG model understates the waiting time assumptions by 5.1 weeks for PCI and 13.4 weeks for CABG and the model should therefore

	Weeks				Mean weeks	Mean days	Mean years	Source
1st OP visit	**0 to 4**	**4 to 8**	**8 to 13**	**>13**				
Cardiology patients (n)	35,260	20,996	20,059	985	6	42	0.11499	NHS waiting time stats
Cardiac surgery patients (n)	401	112	38	1	6	42	0.11499	NHS waiting time stats
Angiography					11.1	78	0.21355	HES 2005-06
Procedure								
PCI					8.0	56	0.15332	HES 2005-06
CABG					9.3	65	0.17796	HES 2005-06
Overall								
PCI					25.1	176	0.48186	HES 2005-06
CABG					26.4	185	0.50650	HES 2005-06

These points are clarified in addendum 7 and FAD section 4.2.22.

		be re-run using the data in Table 4. Table 4. Calculation of overall waiting times for PCI and CABG according to the method of Hawkins, Sculpher and Rothman (2005). *The mean waiting time for 1st out-patients visit is estimated to be 6 weeks. Overall = 1st OP wait + angiography wait + procedure wait.*	
British Cardiovascular Intervention Society		***Combination of Elective and Non-elective Datasets*** • The model combines the incremental costs and utilities from the elective and non-elective models according to the proportion of patients in each of these two categories in the CTC dataset. The CTC proportion of 32.35% non-elective is low compared with the national picture in which 48.5% (BCIS audit figures for 2006) present as acute coronary syndromes. Thus, LRiG's combination of data, based on a single centre, is not representative of the national picture. Thus, in order to ensure accuracy, the model should be revised to include at least a 49% non-elective contribution.	The Appraisal Committees considerations of this point are described in FAD sections 4.3.5 and 4.3.13, see also addendum 7 and FAD section 4.2.23 for clarification of this point.

- Combination of the two datasets according to the proportions of elective and non-elective is not ideal and has the hallmarks of a 'quick fix'. This appears to have led to some inconsistency between the number of stents used given in Table A of Addendum 6' and the number of stents used shown in the separate elective and non-elective datasets in Table A of Addendum 5'. The number of stents per procedure in Addendum 6' should be the same as that resulting from the combination of the separate datasets in Addendum 5' in the proportions of elective and non-elective patients, but it is not. BCIS have re-calculated the mean stents per procedure and the discrepancies are shown in Table 5.

	Elective	Non-elective	LRiG Combined	BCIS Calculated
Proportion	0.6765	0.3235		
Stents per patient				
No risk factors	1.54	1.43	1.54	1.50
Long lesions	1.63	1.42	1.53	1.56
Diabetes	1.56	1.52	1.56	1.55
Small vessels	2.30	2.00	1.66	***2.20***
Long+ Diabetes	1.72	1.54	1.73	1.66
Long + Small	2.53	2.50	2.24	***2.52***
Small + Diabetes	2.67	2.00	2.57	2.45
Long + Small + Diabetes	3.00	2.00	2.63	2.68
Overall	**1.615**	**1.467**	**1.571**	**1.567**

Table 5. Comparison of LRiG's combined 'number of stents per patient' dataset with BCIS's calculation of the same from the separate elective and non-elective groups.

		• Table 5 shows that there are particular differences for small vessels and long lesions + small vessels. It is our belief that the model reflects the stents per patient shown in the column 'BCIS calculated', in which case LRiG's combined parameter values table shown in Addendum 6' is wrong. However, if the combined parameter values in Addendum 6' correctly describes the mean stents per patient for the total elective + non-elective dataset, then ***the model substantially over-estimates the ICER for small vessels and small vessels + long lesions***. LRiG should be asked by N.I.C.E to investigate these questions and issue a clarification. Again wrong imput will result in wrong oconclusions from the model • If the separate datasets prove to be correct, they should be combined in the proportions of 52% elective and 48% non-elective as above and the model re-run on this basis. If the Addendum 6' combined dataset is correct, the model should be re-run using these data.	
British Cardiovascular Intervention Society		***Acute Coronary Syndromes*** • BCIS note that NICE are now consulting on a clinical guideline development for the management of patients with acute coronary syndromes (ACS). It would therefore be appropriate and helpful for the Appraisal Committee to consider ACS patients as a sub-group who may benefit from DES. • The Committee will be aware that ACS patients who receive BMS are already prescribed Clopidogrel for 12 months, so this cost essentially drops out of the model for ACS and is likely to have a considerable impact on the cost-effectiveness of DES. Whilst BCIS do not agree with 'elective' or 'non-elective' as a clinical categorisation of patients, those presenting with ACS tend to do so in the non-elective setting thus 'non-elective'	The Appraisal Committees considerations of this point are described in FAD sections 4.3.10 and 4.3.13; see addendum 7 and FAD section 4.2.22.

		relative risks, costs and resource use are the most appropriate inputs for an ACS model.	
British Cardiovascular Intervention Society		**Summary** • Whilst the LRiG model structure is appropriate to address the cost effectiveness question, a considerable number of data inputs are either questionable, unrepresentative or out of date. The inappropriate use of such inputs, as they currently stand, make any conclusions base don the model wholly unreliable. This is not a good way to construct a National policy – on flawed data • LRiG's model should be re-run using the following data inputs: 1. A 13% repeat revascularisation rate for an unselected population (although it would be possible to argue for a 14.4% level based on the Scottish registry). 2. The literature-based relative risks for the risk factors of long lesions (1.35), small vessels (1.75) and diabetes (1.52). 3. The trial-based DES risk reductions for the overall population (0.60), long lesions (0.70), small vessels (0.69) and diabetes (0.61). 4. DES price premium of £300, reflecting current national pricing. 5. The 2005-06 reference costs. 6. Up to date waiting times, calculated according to the UK-based methodology published by Hawkins, Sculpher and Rothman (2005). 7. LRiG elective and non-elective datasets combined in the	Comments noted. The Appraisal Committees considerations of this point are described in FAD sections 4.3.12, 4.3.13 and 4.3.14; see also addendum 7 and FAD sections 4.2.22, 4.2.23, 4.2.27 and 4.2.28.

		nationally-appropriate proportions of 52% elective and 48% non-elective. 8. Clarified and/or corrected inputs for the mean number of stents per patient. • The cost-effectiveness of DES in patients with acute coronary syndromes should also be modelled to inform the clinical guideline development. The above points on data inputs should be implemented into this model.	
Boston Scientific		Whilst we welcome the opportunity to analyse the Assessment Group's model our view remains, as stated in our previous submissions, that many of the key inputs to the model are not substantiated by the body of clinical evidence on DES. As such, the design quality or otherwise of this model is entirely secondary to the input data which has led to the potentially perverse draft guidance.	DESs are recommended in circumstances outlined in FAD section 1.1.
Boston Scientific		**Application of relative risk** The LRiG model applies the same risk reduction across the total population and the sub-groups (small vessels, diabetes, and long lesions). This is an unrealistic approach as there is overwhelming evidence from RCTs and registries that that DES are particularly effective in certain high-risk subgroups sub-groups. We would urge the Committee to draw from a meta-analysis of RCTs a distinct risk reduction for each high-risk subgroup.	The Appraisal did not accept all the parameters and assumptions in LRiGs model see FAD sections 4.3.4, 4.3.7, 4.3.12, 4.3.13 and 4.3.14. The Appraisal Committee considered BCIS's assumptions see FAD sections 4.2.23, 4.2.28, 4.3.13 and 4.3.14.

Boston Scientific		**Diabetes as a risk factor** In the LRiG model the overall risk factor for Diabetics is 1.19 – a very low number resulting from the combination of elective and non-elective groups. In the non-elective group, Diabetics are shown as having a lower risk factor (0.9) than the general population. This is at odds with the bulk of published evidence which shows diabetes as a significant risk factor. We recommend that the model use a meta-analysis of available RCTs to derive the appropriate figure.	The Appraisal Committee considered BCIS's assumptions see FAD sections 4.2.23, 4.2.28, 4.3.13 and 4.3.14. With regard to diabetes as a risk factor see FAD sections 4.1.23, 4.1.24 and 4.3.4.
Boston Scientific		**Service Costs** The cost inputs used for the model are NHS reference costs 2003/4. These should be updated with the latest published NHS reference costs (2005/6) as there have been substantial changes in this period making the original inputs outdated.	This point is clarified in addendum 7 and FAD section 4.2.22.
Boston Scientific		**Device Costs** The current prices of DES and BMS in the NHS should be gathered to properly identify the true delta between these products. The NHS PaSA survey of prices will be 4 years out of date by the time this guidance is issued and is unlikely to reflect current prices.	The Institute has received data from PASA for 2007/08; see FAD section 3.6.
Boston Scientific		**Average number of stents** There is an attempt to show a differentiated average number of stents across all of the sub-groups and between elective and non-elective cases. The problem	Comments noted. The Committees considerations of this point

		with this approach is that some of the sub-groups represent only 0.1% of the CTC database. As such this cannot be meaningful and we believe that the analysis should be re-run using the overall mean number of stents for all subgroups.	is described in FAD section 4.3.8.
Boston Scientific		**Conclusion** The specific issues shown above relate directly to the opportunity to analyse the Liverpool model at close quarters. We refer you to our consultation response to the ACD to reiterate that LRiGs reliance on single centre non-randomised data and the selective use of literature evidence such as BASKET mean that the inputs to this model regarding absolute risk and relative risk reduction do not reflect the breadth of evidence on DES and as such the results from the model will be perverse. We would therefore recommend to the Committee to refer this Appraisal to the Decision Support Unit.	The Appraisal Committee did not accept all the parameters and assumptions in LRiGs model see FAD sections 4.3.4, 4.3.5, 4.3.6, 4.3.7, 4.3.10, 4.3.11, 4.3.12, 4.3.13 and 4.3.14.
Cordis		**Introduction** Whilst the structure of the economic model seems to include the major costs and effects in the first year after repeat revascularisation, we have major concerns over many of the data inputs, which are either out of date, based on incorrect assumptions, use single centre data where a wider literature exists, or are inconsistent with previous Assessment Report addenda.	Comments noted.
Cordis		**Modelling Methods** Some of the inputs are hard coded rather than being transparently derived from raw data. This specifically applies to the QALY loss awaiting PCI/CABG, the AMI utility gain and the AMI costs saving. The model does not attempt to handle parameter uncertainty using probabilistic sensitivity analysis and therefore LRiG have not followed NICE's Guide to the	Comments noted. The Appraisal Committee considered a one year time horizon to be appropriate see FAD

		Methods of Technology Appraisal. This is a serious limitation. It is possible to estimate confidence limits around many of the data inputs, so we see no reason why LRiG should not have followed this practice. The model does not explore cost effectiveness beyond the first year, probably due to LRiG's view that there are few data points after this time. This is certainly not the case now and given the potential impact of the draft guidance, it would be both diligent and fair to explore the longer-term. This is particularly important given that repeat revascularisations accrue beyond year 1 (thus so does the DES benefit) and the AMI utility gain is similarly so. Furthermore, AMI utility gains will also persist into each subsequent year and these effects are not accounted for within the 1-year time horizon.	section 4.3.6.
Cordis		**DES Price Premium** The economic model investigates DES cost effectiveness at various levels of price premium. Interpretation of the results is critically dependent upon the price premium that the Appraisal Committee decides is representative of the UK. We request, for transparency and methodological reasons, clarification of how the correct DES price premium will be identified. If an average BMS price is used, as appears to be the case in the model, an average DES price should also be used to ensure equity. Averages would also be consistent with the use of NHS reference costs elsewhere in the model, as these are also averages. It should be noted though, that the Institute's Guide to the Methods of Technology Appraisal states that "*Where the actual price paid for a resource may differ from the public list price (for example pharmaceuticals, medical devices), the public list price should be used*" (NICE 2004, section 5.6.1.1). We recognise the desire from the NICE to quote a price that all NHS hospitals can procure at, but NICE should also recognise that not all providers purchase BMS at the same price now. Furthermore, it would be inequitable to use list prices as a source of upper DES price certainty whilst at the same time using market prices for BMS.	The Institute has received data from PASA for 2007/08; see FAD section 3.6.

Cordis		**New UK Data on Proportion of Patients with Acute Coronary Syndromes (ACS)** BCIS recently released data for 2006 showing that the proportion of patients presenting with ACS (i.e. incurring non-elective costs and resource use) has risen to 48.5% (Ludman 2007). This means that the proportions used in the model to combine LRiG's elective and non-elective datasets, and the proportion of DES patients who require 9-months additional clopidogrel, should be revised. The impact of this on individual data inputs is shown below.	The Appraisal Committees considerations of the point are described in FAD sections 4.3.10 and 4.3.13; see also addendum 7 and FAD section 4.2.22.
Cordis		**The Absolute Risk of Repeat Revascularisation with BMS** It is not clear why the absolute risks of repeat revascularisation with BMS have been set at 10% for elective patients and 13% for non-elective patients. The submission to NICE by NHS QIS (dated 13th January 2006) states: *"The Scottish Coronary Revascularisation Register Report for 2003-04 reports a repeat revascularisation rate at 12 months of 12.9% (95%CI 12.1-13.7; n=6525 vs 7.79% in Liverpool) for patients undergoing elective PCI and 16.6% (15.7-17.6; n=5921 vs 10.15% in Liverpool) for patients undergoing PCI for unstable coronary syndromes."* Combining these data in the correct proportions of ACS and non-ACS (48.5% ACS, Ludman 2007), the absolute risk of repeat revascularisation for the combined, unselected population is **14.7%**. The model should be re-run using these Scottish registry data.	The Appraisal Committee did not accept all the parameters and assumptions in LRiGs model see FAD sections 4.3.4, 4.3.6, 4.3.12, 4.3.13 and 4.3.14. The Appraisal Committee considered BCIS's assumptions see FAD sections 4.2.23, 4.2.28, 4.3.13 and 4.3.14.
Cordis		**The Risk Reduction Associated with DES** The model presents alternatives of 55% and 65% risk reduction associated with DES. This is not representative of the trial data pertaining to Cordis's Cypher Sirolimus-eluting Stent. This means that for the Cypher stent, the non-fatal MI QALY saving of 0.00055 used in the model is an under-estimate and should be revised to 0.0013502.	The Appraisal Committee did not accept all the parameters and assumptions in LRiGs model see FAD sections 4.3.4, 4.3.7, 4.3.12, 4.3.13 and 4.3.14.

		(Calculation: absolute MI saving of 0.86% x (utility of CHD 0.84 (Hawkins et al 2005) - utility of MI year 1 0.683 (Jones et al 2004)).	The Appraisal Committee considered BCIS's assumptions see FAD sections 4.2.23, 4.2.28, 4.3.13 and 4.3.14.
Cordis		**Relative Risks for the Independent Risk Factors** The model employs an unusually low relative risk (RR) for diabetes of 1.19, which results from the sole reliance on the CTC database and a combination of relative risks of 0.90 for non-elective patients and 1.38 for elective patients. The non-elective RR appears to be spurious because a RR of <1 for a risk factor that has repeatedly been shown to increase the relative risk is perverse. It would be more reasonable the use the relative risks for the individual risk factors previously submitted by BCIS as they are derived from the wider literature and are not solely reliant upon the CTC database.	The Appraisal Committee was aware of the views expressed by consultees and commentators about the CTC database. Therefore it did not accept all the parameters and assumptions in LRiGs model see FAD sections 4.3.4, 4.3.7, 4.3.12, 4.3.13 and 4.3.14. The Appraisal Committee considered BCIS's assumptions see FAD sections 4.2.23, 4.2.28, 4.3.13 and 4.3.14.
Cordis		**NHS Reference Costs** The model uses reference costs from 2003-04, which are out of date, as the Department of Health has now published costs for 2005-06. Table 1 compares these two sets of costs. The 2003-04 data under-estimate the costs associated	This point is clarified in addendum 7 and FAD section 4.2.22.

<table>
<tr>
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<td>with repeat revascularisation and thus render the current model inaccurate. The model should be re-run using 2005-06 reference costs.

<table>
<tr><th>Item</th><th>2003-04 Reference Cost</th><th>2005-06 Reference Cost</th><th>Difference</th></tr>
<tr><td>Cardiology 1st out-patient attendance</td><td>£134</td><td>£148 (code 320F)</td><td>+£14</td></tr>
<tr><td>Cardiac surgery 1st out-patient attendance</td><td>£208</td><td>£274 (code 172F)</td><td>+£66</td></tr>
<tr><td>Cardiology out-patient follow up</td><td>£94</td><td>£104 (code 320F)</td><td>+£10</td></tr>
<tr><td>Cardiac surgery out-patient follow up</td><td>£156</td><td>£182 (code 172F)</td><td>+£26</td></tr>
<tr><td>Angiography</td><td>£724</td><td>£838 (day case E14)</td><td>+£114</td></tr>
<tr><td>PCI (elective)</td><td>£2609</td><td>£3093</td><td>+£484</td></tr>
<tr><td>Unstented PCI</td><td>£1453</td><td>£1937</td><td>+£484</td></tr>
<tr><td>CABG (elective)</td><td>£7066</td><td>£8172</td><td>+£1106</td></tr>
</table>

Table 1. Comparison of 2003-04 reference costs used in the LRiG model and the latest 2005-06 reference costs</td>
<td></td>
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<td>Cordis</td>
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<td><u>Calculation of QALY Loss Awaiting Repeat Revascularisation.</u>
LRiG calculation of QALY loss awaiting repeat revascularisation is based on a 16 week wait for PCI, a 9 week wait for CABG and an assumed 4 week wait prior to joining the list. These are derived from NHS waiting time statistics for quarter 4 2004-05, and are again out of date, as the Department of Health has</td>
<td>This point is clarified in addendum 7 and FAD section 4.2.22.</td>
</tr>
</table>

		published waiting time statistics up to the 4th quarter 2006 and HES data for 2005-06 (see 8.3). The waiting time for PCI and CABG procedures should be taken from HES data rather than the less specific NHS waiting times statistics. DES data give a specific mean waiting time for PCI and CAB procedures rather than, for example the entry for 'cardiothoracic surgery' in the NHS waiting time statistics. Cardiothoracic surgery includes other, non-revascularisation procedures and is therefore not specific. LRiG's formula for estimating total waiting times is somewhat imprecise compared to the method published by Hawkins et al (2005). Hawkins et al considered the total wait to be made up of three elements: time waiting for first consultant appointment, time waiting for coronary angiography and time waiting for the revascularisation procedure. Latest data from the Dept. of Health suggests that these inputs should be: 6 weeks for 1st cardiology/cardiac surgery out-patient attendance (waiting time statistics, Q4 2006), 11.1 weeks waiting for angiography (HES 2005-06), 8.0 weeks waiting for PCI procedure and 9.3 weeks waiting for CABG procedure (HES 2005-06). The model should be re-run using the Hawkins formula and the data given above.	
Cordis		**<u>Combination of Elective and Non-elective Datasets</u>** The combination of the incremental costs and utilities from the separate elective and non-elective models should be according to the national proportion of 48.5% non-elective, rather than the single centre, CTC proportion. LRiG should also explain the discrepancy between the number of stents per procedure in their combined Table A of Addendum 6' and the number of stents shown in the separate elective and non-elective datasets in Table A of Addendum 5'. Combining the individual datasets in the proportion LRiG propose does not produce the results they report in Table A of Addendum 6'. It is our belief that Table A of Addendum 6' is incorrect, where the number of stents per procedure appears to be particularly inaccurate for small vessels and	The Appraisal Committees considerations of the point are described in FAD sections 4.3.5 and 4.3.13.. See addendum 7 and FAD sections 4.2.23 for clarification of this.

		long lesions + small vessels. However, if Table A of Addendum 6' is correct (1.66 stents per procedure for small vessels and 2.24 for small vessels + long lesions) and the individual elective and non-elective number of stents per procedure are wrong, then the model overestimates the ICERs for small vessels and long lesions + small vessels in particular. The Institute will note that Cordis raised this issue on 1st August, but the subsequent 'clarification' issued to consultees did not resolve the query. These key inputs should be checked and the correct data should be entered into the model.	
Cordis		**<u>Acute Coronary Syndromes</u>** NICE's announcement of the development of a clinical guideline for the management of patients with ACS and the stated relevance of the guidance on the use of coronary stents to that guideline, suggests that ACS should be considered as an additional sub-group within this Review. There are clinical and economic grounds for considering ACS in that the 16.6% repeat revascularisation rate for these patients shown in the Scottish registry gives cause to believe that there may be substantial benefit from DES in this population. Secondly, ACS patients receiving DES do not require 9m additional Clopidogrel for reasons previously stated and accepted by the Appraisal Committee. This removes a major cost item from the model and is likely to have a major impact on the ICER for ACS patients. BCIA have previously shown that ACS and unstable angina do occur in the literature as independent risk factors for repeat revascularisation (BCIA response to Assessment Report Addendum), and that the risk increase for unstable angina is of a similar order to that for long lesions (odds ratio ~ 1.40). One study (Gotschall et al 2006) reported an odds ratio for target vessel revascularisation of 3.23 for ACS. We propose that ACS be added as an additional sub-group for consideration,	The Appraisal Committees considerations of the point are described in FAD sections 4.3.10 and 4.3.13. See also addendum 7 and FAD section 4.2.22.

		with modelling based on non-elective reference costs and resource use, as these patients present in the non-elective setting.	
Cordis		**Assumption of a DES Class Effect** The model assumes that all DES confer an equal treatment effect for reductions in both repeat revascularisation and MI. This is not a valid assumption. The Appraisal Committee will note that Stettler et al (2007) have shown a 30% reduction in TLR for Cypher versus Taxus (HR 0.70, 95%-CI 0.56-0.84, p=0.0021), a finding which has been confirmed by Schömig et al (2007) using patient-level data (HR 0.72, 95% CI 0.61 to 0.86, p < 0.001). Stettler et al also recorded a significant difference in MI rates between the two DES in favour of Cypher (HR 0.83, 95%-CI 0.71-1.00, p=0.045), an effect that Schömig et al found strongly echoed in the patient-level data (HR 0.81, 95% CI 0.64 to 1.02, p = 0.07). This difference becomes even more pronounced after the first year (HR 0.45, 95% CI 0.25 to 0.80, p=0.006).	The Appraisal Committees considerations of the point are described in FAD section 4.3.3.
Cordis		**Wider Impact on the National Health Economy**	Comments noted. DESs are recommended in circumstances outlined in FAD section 1.1.

Whilst the model is not intended to provide budget impact estimates, the Institute should be mindful of the impact that DES use has had on the NHS. Figure 1 shows the evolution of NHS reference costs for PCI and CABG, as well as the waiting times for each of these procedures. The reference costs have been inflated to 2007 values using the Health Service Cost Index.

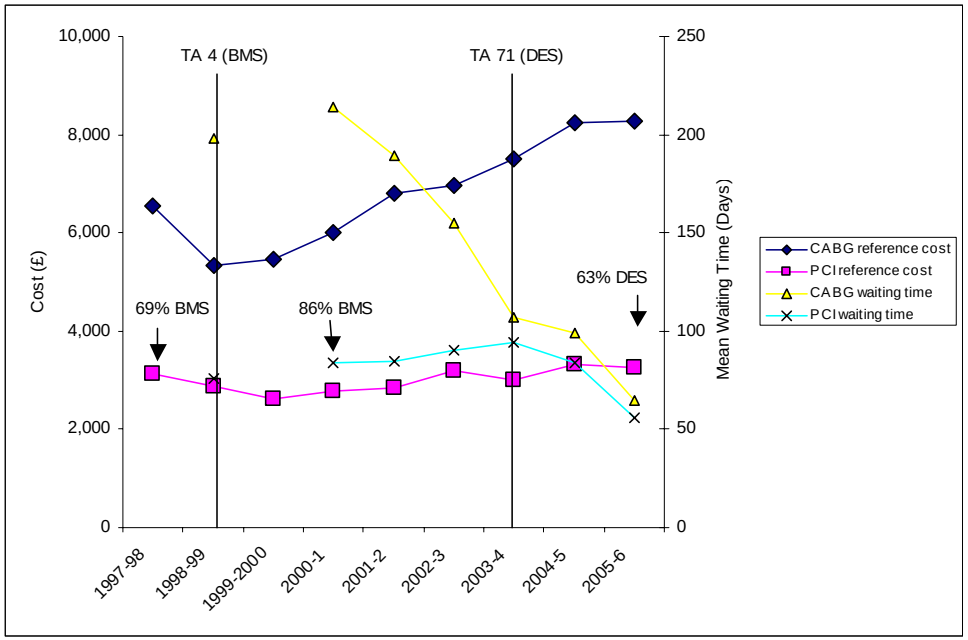

Figure 1. **Evolution of NHS reference costs and waiting times for PCI and CABG over time.** *Reference costs have been inflated to 2007 values. The reference cost for PCI fell by 1.6% between 2004-05 and 2005-06. TA = issue of NICE guidance on the use if stents resulting from technology*

		appraisals. Figure 1 shows that the growth in the use of stents in general and the introduction of DES has had very little impact on the NHS procedural cost of PCI. Most notably, the PCI reference cost fell by 1.6% in real terms between 2004-05 and 2005-06, probably reflecting the fall in both BMS and DES market prices that we have outlined in previous submissions. The Institute should consider carefully the impact of the current draft guidance in the light of these data. The potential swing from PCI (with a falling cost to the NHS) to CABG (with an increasing cost to the NHS) is likely to impose a net burden on the NHS of £55.2 million in 2008 alone.	
Cordis		**Summary** The model should be re-run incorporating: • A clear and transparent determination of the average DES price premium. • Data inputs revised based on a proportion of 48.5% non-elective patients. • 14.7% repeat revascularisation rate from the Scottish registry. • The trial-based absolute risk reductions for the Cypher stent published by Stettler et al (2007). • The relative risks for the individual risk factors identified by BCIS. • The latest NHS reference costs (2005-06). • QALY loss based on the latest NHS waiting time data and waiting times calculated according to Hawkins et al (2005). • Clarification of the correct number of stents per procedure, especially for small vessels and small vessels + long lesions. • ACS as a separate risk factor group. • Separate TLR and MI risk reductions for Cypher and Taxus. Cordis urge the Institute to address all of the limitations of the economic model highlighted in this commentary. The outcome of the Review would be perverse	Comments noted. The Appraisal Committees considerations of the point are described in FAD sections 4.3.12, 4.3.13 and 4.3.14. See also addendum 7 and section 4.2.22, 4.2.23, 4.2.27, 4.2.28.

		if it were based on such out of date, unreliable and questionable inputs.	
Medtronic		Thank you for the opportunity to review the electronic copy of the assessment group's model for the appraisal of drug eluting stents (DES). We believe it has added value to the consultation process. Medtronic's comments are based on the protected version of the economic model provided by NICE and the NICE TAR 04/42 Version 3 and associated appendices We would like to address our concerns on the technical aspects of the model und eleven key headings in line with the core principles of economic modelling and HT Model design, replicability of the model, structural assumptions, strategies/comparators, time horizon, data inputs, model layout, uncertainty, intern consistency, external consistency and specific DES issues.	Comments noted.
Medtronic		**Model design** The spreadsheet shows the model to be a very basic decision tree model. It is described within ten formulae in the TAR (page 104). Whilst we agree that models should not be unnecessarily complicated, we do not believe that the assessment group's model is sufficiently sophisticated to allow adequate analysis of the cost-effectiveness of DES.	Comment noted.
Medtronic		**Replicability of the model** As previously mentioned, the model provided was protected and it was therefore not possible to examine the formulae. We believe that as independent assessors, the Liverpool group's model should be subject to the same level of scrutiny as the models of other stakeholders who are required to submit unlocked versions which can be independently replicated to ensure there are no errors. Despite the model being locked down, it has been possible to replicate the	Comments noted. See section 4.4.1.9 of the technology appraisal process guide with regard to read-only versions of the model.

		model via referral to the assessment report and through trial and error of including and excluding variables to match the results in the protected model. On the basis of this replication we do not believe that the report description accurately reflects the apparent formulae used in the Liverpool model. We request that the Liverpool group check the report wording in case of any potential errors.	
Medtronic		**Structural assumptions** Through our replication of the model, we believe that the structural assumptions are not as transparent as they appear in the TAR. The structural assumptions appear only to be relevant if a twelve month time horizon is deemed appropriate. Mortality does not appear to be taken into account within the model. The justification for this is that three year data is inconclusive between DES and BMS. However, if this had been incorporated it would have allowed the appraisal committee to see whether any short-term mortality data or future mortality data would have an effect on the guidance being proposed. Other clinical outcomes evaluated in trials submitted to the Institute included acute MI, other coronary events and vessel failure. These have not been modelled as the authors found no difference between DES and BMS in a meta-analysis. We believe that the appraisal committee should consider whether these outcomes are relevant. By excluding them, the validity of the model from a clinician perspective may be compromised. It should be noted that meta-analyses do provide uncertainty over the point estimate and that this can be examined through probabilistic sensitivity analysis (PSA) within a modelling framework (the authors do not do this).	Comments noted. The Appraisal Committee considered a one year time horizon to be appropriate see FAD section 4.3.6. . The Appraisal Committees considerations with regard to mortality are described in FAD section 4.3.2.

Medtronic		**Strategies/comparators** The Liverpool model has been built based on immediate data constraints (some of which have now been overcome due to the delays in the appraisal process and newly available data). The critical appraisal of decision-analytical models for HTA (Phillips et al. 2004) clearly states that options should not necessarily be constrained by data availability. We suggest that due to process delays a re-evaluation of data currently available and its appropriateness for inclusion in the model should be mad and assumptions tested.	Comments noted.
Medtronic		**Time horizon** A twelve month time horizon has been chosen by the assessment group, however, the clinical literature suggests that differences in the effect and consequences between the comparators may extend beyond this. The authors note that there is limited long term data available, however make no attempt to handle this within the model and therefore the model has limited applicability to HTA decision-making. One of the powerful uses of pharmacoeconomic modelling is being able simulate what may happen over time. The design of the Liverpool model would need to be changed to allow this level of analysis which we believe is required. It is surprising that, given uncertainty of long term effects, the assessment group did not attempt longer term modelling and employ value of information techniques to see if collecting longer term outcome data (possibly through a multi-centre registry) was of value. By not modelling over the longer-term, the model is in essence inflexible and cannot provide a benchmark to show what DES has to achieve to be deemed cost-effective. Lack of data (particularly with new technology) does not necessarily mean no effect. We believe that models developed as part of a	The Appraisal Committee considered a one year time horizon to be appropriate see FAD section 4.3.6.

		NICE appraisal should have the capacity to be able to simulate potential future benefits.	
Medtronic		**Data** Comprehensive data input information is included in the BCIA model comments with which Medtronic concur. Top-line, despite the numerous RCTs available at the time of review, the assessment report authors have consistently relied heavily on observational, single centre audit data. As previously commented to the Institute, such data is prone to bias and we believe does not accurately reflect the true effect of DES: A. Patient selection bias – treatment with DES or BMS may be based on patient characteristics and this can affect the reason for differences in effect B. Single centre – treatment may not accurately reflect that of other centres and therefore applying the effect from this centre to others may be inappropriate. Again, we would also like to highlight that due to delays in the appraisal process valuable new data is available which should be considered as part of this appraisal.	Comments noted. The Appraisal Committee did not accept all the parameters and assumptions in LRiGs model see FAD sections 4.3.4, 4.3.5, 4.3.6, 4.3.7, 4.3.10, 4.3.11, 4.3.12, 4.3.13 and 4.3.14. The Appraisal Committee considered BCIS's assumptions see FAD sections 4.2.23, 4.2.28, 4.3.13 and 4.3.14.
Medtronic		**Model layout** Medtronic is disappointed with the quality of model lay out and the fact that no referencing is presented. It would seem that some of the inputs may be hard coded rather than derived from other clearly inputs (for example, derivation of disutility values). However, as the model was locked down, this is not possible to confirm conclusively.	Comments noted.

		It is also disappointing to see that the model does not clearly show the total costs and total QALYs for each strategy before concluding the incremental costs and benefits. Although the ICER only relies on incremental results, good modelling practice recommends that costs and QALYs should be reported separately for each strategy.	
Medtronic		**Uncertainty** The authors rely heavily on the use of basic deterministic sensitivity analysis. They have made limited attempts in handling uncertainty: 1. Changes in methodological assumptions 2. Structural uncertainty e.g. long term effect/modelling has not occurred 3. Heterogeneity – sub group analyses (published literature suggests that there are specific sub-groups where DES are more cost-effective) 4. Parameter uncertainty is not appropriately handled through PSA Contrary to NICE guidance and current thinking within the pharmacoeconomic field, the authors have not addressed parameter uncertainty through PSA. It is of concern that the independent assessment group are not following NICE guidance on this.	Comments noted.
Medtronic		**Internal consistency** It has not been possible to conclusively confirm internal consistency of the mathematical logic – although replication of the model has been done, there seems to be differences between reported structural equations in the report and the equations in the model.	Comments noted.
Medtronic		**External consistency** It is not clear whether the authors have included all relevant data within their	Comments noted.

		model. It would appear that the main data incorporated is that of the single centre audit in Liverpool. It has not been possible in the time constraints to test external consistency fully with other data sources. However, it is likely that the model structure is not sufficient to model some of the other data available, particularly that showing effects beyond 12 months. Additionally, the assessment group has only examined data for two stents. This is out of line with the current evidence base	The Appraisal Committee considered BCIS's assumptions see FAD sections 4.2.23, 4.2.28, 4.3.13 and 4.3.14. See section 4.3.3 for the Appraisal Committee's considerations of the comparison between different types of DESs.
Medtronic		**DES issues** The authors do not use list prices for the stents. The average number of stents used also differs between manufacturer's submissions and the assessment group submission. It would appear that there is uncertainty around this assumption which should be tested.	Comments noted. The Institute received 2007/08 data from PASA with regard to price; see FAD section 3.6. See FAD section 4.3.8 with regard to the average number of stents used.
Medtronic		**Conclusion** In conclusion, despite the concerns regarding the lack of modelling techniques employed by the assessment group, the applicability of the results to national policy making relies mainly around the findings from a non-randomised, single centre audit. Where there is any concern about the generalisability of this data (including average number of stents), particularly when RCT data is available, extreme caution should be placed on the results provided by the model. With regards to the modelling techniques employed, it would appear that the	Comments noted. The Committee did not accept all the parameters and assumptions in LRiGs model see FAD sections 4.3.4, 4.3.5, 4.3.6, 4.3.7, 4.3.10, 4.3.11, 4.3.12, 4.3.13 and 4.3.14.

		simple model may be appropriate for evaluating short term effects. However, if the clinical community believes that there are potential long term benefits of DES (particularly if revascularisation differences are likely to occur in the future), the model has limited use. It is also noted that the model does not fully comply with current NICE guidance and good practice guidelines, particularly in the handling of uncertainty and ability to validate the structure. On the basis of this model review and in view of the fact that new data is available on DES which would add value to the appraisal if considered, we would like to reiterate our suggested next steps submitted to the Institute as part of the ACD consultation. We maintain that the most appropriate solution would be for a complete re-analysis of the clinical and cost-effectiveness section of the AR. Due to the conflict of interest of the Liverpool group regarding DES and their publication record we believe an alternative group would be most appropriate to conduct any new assessment. As an alternative, as previously suggested to the institute, the Decision Support Unit (DSU) could be engaged to objectively review the work of the Liverpool group.	The Appraisal considered BCIS's assumptions see FAD sections 4.2.23, 4.2.28, 4.3.13 and 4.3.14.

Commercial in Confidence data was also received but has not been included in the table.

The following consultees/commentators indicated that they had no comments on the ACD
Action Heart
Royal College of Nursing

[i] http://www.tctmd.com/csportal/appmanager/tctmd/ebmc?_nfpb=true&_pageLabel=EBMCenterHome&hdCon=1310638&srcId=1&destId=53

[ii] Bagust A, Grayson AD, Palmer ND, et al. Cost effectiveness of drug eluting coronary artery stenting in a UK setting: cost-utility study. *Heart* 2006 92:68-74. *originally published online on 14 April 2005*

[iii] Brunner-La Rocca, Kaiser C, Pfisterer M, et al. Targeted stent use in clinical practice based on evidence from the BAsel Stent Cost Effectiveness Trial (BASKET). Eur Heart J 2007;28:719-25

[iv] http://www.theheart.org/printArticle.do?primaryKey=556107

[v] Thomas M. Are drug eluting stents really worth the money? *Heart* 2006;92:5-7.

[vi] Kaiser C, Brunner-La Rocca HP, Buser PT, et al. Incremental cost-effectiveness of drug-eluting stents compared with a third-generation bare-metal stent in a real-world setting: randomized Basel Kosten Effektivitats Trial (BASKET). Lancet 2005;366(9489):921-9