Reetan Patel
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71 High Holborn
London WC1V 6NA

10 May 2007

Dear Reetan,

Ischaemic Heart Disease – coronary artery stents – appraisal number 71
Extra analyses (2) for Ischaemic Heart Disease – Coronary Artery Stents– ACD meeting July 2007

Please find attached comments from Boston Scientific in response to the extra analysis from LRiG requested by the Appraisal Committee.

If there are any questions or clarifications needed, please do not hesitate to contact me either by e-mail or by telephone.

Yours sincerely,

Director Health Economics and Public Affairs
Boston Scientific Ltd

Additional Analysis:
Assessing the Impact of prolonged Clopidogrel on Cost-Effectiveness

Considering the uncertainty around optimal duration of clopidogrel post-PCI, we believe that the impact on cost-effectiveness in this additional analysis - as commissioned by NICE to the Liverpool Review Group (LRiG)- to be potentially misleading.

Our comments fall into two categories: first that the analysis does not rely on an evidence base (nor has this been investigated), and second that it is not clear that the flaws in the initial analysis by the LRiG have been addressed. The sections below will deal with each of these in turn.

Evidence Base for Clopidogrel Duration

1. There is no evidence base on the optimal duration of clopidogrel use; in fact, the debate on use of clopidogrel post-PCI is still underway. Therefore, there is no definite evidence to support 12 months Plavix for all DES patients. The FDA statements suggest that labelling for both approved DES should include reference to the ACC/AHA/SCAI PCI Practice Guidelines, which recommend that patients receive aspirin indefinitely plus a minimum of 3 months (for the Cypher™ Stent patients) or 6 months (for TAXUS™ Stent patients) of clopidogrel, with therapy extended to 12 months in patients at a low risk of bleeding. The continuation of clopidogrel therapy is therefore not compulsory and remains a decision to be made by the consultant on a case by case basis and will not apply to 100% of DES patients.

2. Moreover, the prolonged antiplatelet therapy period is not limited to DES patients. Around 60% of PCI cases are emergent, a group that are effectively acute coronary syndromes (ACS) patients. The ACS guidelines cover these patients for 1 year of Plavix anyway, regardless of the type of stent (BMS or DES).

3. According to clinical debates and the literature, it appears that in practice there is not a clear distinction between DES and BMS patients regarding duration of clopidogrel therapy. Other cost-effectiveness analyses, including the initial LRiG report, have actually excluded clopidogrel costs from their model due to the difficulty to define explicit treatment duration according to the type of stent placed.

The Boston Scientific economic model looked at the impact of 12-month anti-platelet

therapy in the sensitivity analysis. Perhaps not surprisingly, the results were highly sensitive to the clopidogrel duration. It is critical that the analysis is based on a supported, consensus based value.

4. Finally, a related issue raised in this debate is patient compliance. Regardless of the optimal duration for clopidogrel use, there is a danger that benefits will not be seen felt by patients or the system due to poor patient compliance.

A. Original LRiG Analysis

The latest NICE communication included addendum 3 of the Liverpool Group Assessment report. It was unclear from the tables whether any amendments to the methodology, reflecting our comments from January and April 2006, have been addressed. Our letters from those dates are attached for reference. We have expressed our concerns about the methodology, approach, and potential bias in the LRiG report and - until those questions are addressed - any additional analysis will only compound previous flaws.

Cathryn Fuller
Project Manager
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Mid-City Place
71 High Holborn
London WC1V 6NA

12 January 2006

Dear Cathryn,

Ischaemic Heart Disease – coronary artery stents – appraisal number 71

With reference to the assessment report produced by the LRiG, please find Boston Scientific Ltd.'s initial comments on the content of the report.

If there are any questions or clarifications needed, please do not hesitate to contact me either by e-mail or by telephone.

Yours sincerely,

Public Affairs Manager UK & Ireland
Boston Scientific Ltd

Contents:

1. Executive Summary

The Assessment report from the LRiG does not represent a wholly balanced view of the body of evidence pertaining to the clinical- and cost- effectiveness of DES and contains some omissions regarding available data as well as some contentious statements that will be challenged in this document.

A paper by Bagust *et al* [1], on which much of this report is based has been comprehensively challenged by Dr Martyn Thomas[2], and by the BCIA at the time of publication and these responses are well-documented. Concerns regarding the methods and conclusions of the Bagust *et al*. paper consequently remain in terms of this AR, and call into question the impartiality of the AR in this field. There is a concern regarding conflict of interest with the LRiG approach. A publication in *Heart* by Bagust *et al* applies a similar approach and raises the question of potential bias.

In section A of our response we will demonstrate that the two DES products assessed in the original guidance (TAXUS® and Cypher®) show no statistical clinical difference in efficacy when the one clinically relevant large multi-centre RCT (REALITY) is analysed. Whilst single-centre or less-robust studies may be useful in understanding variations in local treatment practice or identification of patients of interest, their use is limited without the support of a large, well-designed RCT. As NICE guidance has such an impact on clinical practice in the NHS and beyond it is vital that accurate and supportable statements, based on the best available evidence, are made in relation to available products.

In section B of our response, we will demonstrate that the overall economic evaluation conclusions rely on acceptance of the outlier CTC risk reduction results, the methodology of estimating effectiveness, and the definition of risk factors. The approach taken is flawed from critical aspects and is in conflict with the international literature as well as the previous guidance issued by NICE.

In section C, we urge the committee to differentiate between stents supported by large scale clinical trial programmes and those that are not. We also present initial evidence that there may be a clinical differentiation of the TAXUS and CYPHER stents compared with other DES entering the market.

On page xvi of the AR the authors state that evidence of 70% usage of DES (in compliance with original NICE guidelines) is “anecdotal.” In fact this estimate is in line with a peer-reviewed abstract[3] based on research in a real-world NHS setting in Birmingham, as well as a publication based on research in Southampton [4].

In addition, in section 9.3 the authors state that there has been a 'rapid, uncontrolled expansion of demand in the UK'. This cannot be substantiated as the major control mechanism has in fact been the original NICE guidance which has influenced both clinical practice and the availability of funding for DES in the NHS. The statement that 'the suppliers…have little incentive…..to compete effectively with each other' is patently not the case. Aggressive price and service competition has brought about price reductions from when the first DES was launched in the UK market and suppliers continue to work in a highly competitive environment where every point of market share is keenly contested. The result of this is that NHS patients have access to high-quality products, supported by comprehensive clinical trials, and clinicians and Trusts enjoy high service levels and value-added support. This is not the behaviour that is associated with an uncompetitive market.

Finally, in the last section we note minor comments on corrections, naming, wording, and consistency within the report.

2. MAJOR COMMENTS

A. **Section 5** ***Review of Clinical Effects – Comparison between DES***

As the Boston Scientific original submission to NICE states, clinical differentiation between stents must be based on adequate quality data, e.g. a randomized controlled trial. Clinical evidence on DES has grown substantially since the previous NICE guidance, providing valuable insight into the DES vs. DES debate not previously available. However, the quality of the data must be confirmed before its use in decision-making.

There are two essential limitations to the analysis of DES vs. DES:

1. The report's grading of the studies included in the analysis does not adhere to accepted grading criteria for clinical studies and strength of evidence.

2. There is no evidence that definitively favours one DES over the other. The conclusion in the report that the sirolimus-eluting CYPHER stent had better outcomes for TLR than the paclitaxel-eluting TAXUS stent is incorrect because it:

   a. is based on studies that were poorly designed and conducted;

   b. is based on studies that show conflicting results;

   c. does not include studies that should have been included.

Accordingly, we strongly recommend that NICE clearly state the equivalence between the TAXUS and CYPHER DES rather than give readers a false impression based on an inappropriate level of evidence. Below is additional discussion and details in support of comments above.

A.1. Grading of Evidence

While the LRiG has applied a standard checklist to assess the quality of clinical trials included in this analysis section, it is limited by not being cardiology specific. Perhaps unique to interventional cardiology, there are several specific checklists to assess the quality of clinical trials. Application of cardiology-specific checklists:

- Maintains a common standard for clinical trials to be compared;
- Identifies specific clinical quality checks to the field;
- Applies evidence-based medicine (EBM) to clinical evaluation;
- Attaches the appropriate significance to a medical device used in the field.

Both the ***European Society of Cardiology*** (ESC, March 2005) and the joint ***American College of Cardiology – American Heart Association – Society for Cardiovascular Angiography*** (ACC/AHA/SCAI, November 2005) have issued guidelines for the use of DES. The ESC Guideline published this year devotes a substantial section on DES, and states that evidence-based recommendations for use of DES must focus on the enrolment criteria of controlled, randomized, adequately-powered trials for further clinical guidance.

In 2005, an EBM system for assessing clinical trials (the Silber Score) was developed by the ESC. It allows a pragmatic assessment of the quality of clinical trials. At the 2005 TCT conference Dr. Keith Dawkins addressed the question of comparing TAXUS® with CYPHER®. Therefore, the analysis should be revised to reflect the recent landmark discussions in the cardiology community regarding optimal clinical study design and conduct.

These authorities agree on the important aspects of clinical trials from which to draw firm conclusions; included are a number of characteristics not accounted for in the standard NICE checklist. The details of these sources are presented below. Any or all of these trial assessment approaches should be used for a scientifically valid assessment specific to DES technology.

a) European Society of Cardiology (ESC) 2005 Guidelines for Percutaneous Coronary Interventions (PCI) points out three important characteristics that give confidence to study results: 1) randomized, controlled trials, 2) inclusion of a clinical primary endpoint, and 3) adequate statistical power[5].

b) Silber Score, which ranges from 0 to 10, was developed by European Society of Cardiology[6]. It includes the following 8 characteristics of clinical trials:

1. Clinical Primary Endpoint
2. Double-Blind
3. Evaluation Interval of Primary Endpoint $\geq$ 6 months
4. Multi-center (at least 3 centers)
5. Clinical Events Committee / Data Safety Monitoring Board independent of Steering Committee
6. Primary Endpoint Reached
7. Power of $\geq$ 80% for Primary Endpoint Achieved
8. Follow-up Percentage $\geq$ 80% for Angiographic Primary Endpoint or Follow-Up Percentage of $\geq$ 95% for Clinical Primary Endpoint

A.2. Evidence

The report's conclusion suggesting that the sirolimus-eluting CYPHER stent should be favoured over the paclitaxel-eluting TAXUS stent is incorrect and misleading. We highly recommend that NICE clearly state the equivalence between the TAXUS® and CYPHER® DES.

Definitively answering the question of superiority of one platform versus the other must be addressed through prospective, double-blinded, randomized, multi-centre trials because only such trials can provide the level of evidence accepted by professional organizations like the ESC, ACC, and AHA, and to develop treatment guidelines. The only head-to-head study comparing different DES to date that meets these criteria is REALITY, sponsored by Cordis Corporation, Johnson & Johnson. Comparing CYPHER® versus TAXUS® in 1353 patients treated in >80 centers in 25 countries across 3 continents, REALITY has clearly demonstrated comparable clinical outcomes (including TLR and binary restenosis) for TAXUS® and CYPHER®; failing to meet its original primary endpoint of CYPHER® superiority.

The use of meta-analysis from small studies with under-powered sample sizes can result in inappropriate conclusions; it compounds the results of initial weak studies. The report does not clearly present the inadequacies of such weak, misleading meta-analysis studies; these studies do not have either the strength or stability of evidence to make any claim favouring the sirolimus-eluting stent. The DES meta-analysis studies cited in the report are flawed for the following reasons:

- Poor clinical study design and conduct of individual clinical studies included in analysis (as reviewed above);
- Conflicting results;
- Potential of bias;
- Missing reports from the analysis.

Dr. Gregg Stone of the Cardiovascular Research Foundation discussed this issue at Transcatheter Cardiovascular Therapeutics 2005 conference. In his address, Dr. Stone stated that the existing studies comparing CYPHER® and TAXUS® were very frequently underpowered, had ineffective blinding, and had yielded no consistent conclusions. *"The studies completed to date comparing CYPHER® and TAXUS® are irreconcilably inconsistent and conflicted given their relatively small sample sizes and (in all but one case) non multi-centre design. What is needed is a 'mega-trial' comparing CYPHER® vs. TAXUS® (clinical endpoints only) in an 'all-comer, real-world' patient population (enriched with diabetics and complex lesions) to resolve comparative safety and efficacy issues."*

Studies in Analysis Show Conflicting Results

After establishing comparable safety and superior efficacy of drug-eluting stents over bare metal stents through numerous *randomized, double-blinded, multi-centre trials* including more than 5000 patients, comparison of clinical outcomes between different DES platforms is one of the most relevant questions for practicing interventional cardiologists.

The studies chosen to address these important questions are *non- or single-blinded, single-centre experiences* (including SIRTAX, TAXi, BASKET, CORPAL, DOMINO, ISAR-TEST and ISAR-Diabetes) that fail to meet field-accepted grading criteria. Therefore, these studies do not provide credible data to guide informed decision-making. For example, these studies have resulted in conflicting findings[7].

- SIRTAX, a study including 1012 patients [503 patients received sirolimus-eluting stent (SES); 509 patients received paclitaxel–eluting stent (PES)] reported fewer MACE event for SES as compared to PES.
- TAXi (100 PES patients; 102 SES patients) showed *no treatment differences between TAXUS® and CYPHER®* (MACE: 7% PES vs. 8%SES; p=NS) at one year.
- ISAR Diabetes (103 patients with PES; 102 patients with SES) reported a higher in-segment late luminal loss for PES compared to SES at nine months, but this did not result in a significant higher TLR rate for PES (12% PES vs. 6.4% SES, p=0.13).

Dr. Keith Dawkins compared CYPHER® and TAXUS® in Complex Lesion Subsets, identifying several criticisms of the SIRTAX study, including the following[8]: single blind trial, two centre study, randomization using sealed envelopes, low rate of angiographic follow-up (540/1012, 53.4%), angiographic and non-angiographic follow-up groups not matched, SES and PES angiographic follow-up groups not matched, no angiographic core lab (stent type easily identified), stent thrombosis required ACS *plus* angiographic documentation of vessel occlusion / thrombus, and 'ischemia driven TLR', but TLR anyway if 70% restenosis without ischemia." A number of these criticisms are reflected in the Silber Score above.

The use of non-independent, centre-based angiographic core laboratories within some of these single-or dual-centre trials (SIRTAX, ISAR Diabetes) has further confused the picture. SIRTAX and ISAR Diabetes, for example, report in-segment late loss numbers which are higher than the in-stent results. This is in conflict with all previously reported findings derived from multi-centre studies using well-established, independent, international core laboratories with standardized gold-standard methodologies.

In the REALITY Trial, the 12-month MACE rate were the same for TAXUS® and CYPHER® (11.4%, 10.7% respectively, p-value = 0.73), with comparable TLR rates (6.1%, 6.0% respectively, p-value= 1.0). The endpoint, supporting superiority of CYPHER, was not met in the study.

A publication by Silber has reviewed available trials against criteria, concluding that there is no supportable evidence to demonstrate superiority of one stent over another[9]. The paper by Silber reinforces the point of needing clinically relevant data:

"Of the four studies comparing Cypher stents to Taxus stents, one did not define the primary endpoint (TAXi), two assumed superiority of the Cypher stent (REALITY with a surrogate endpoint and SIRTAX, a single centre study), and one was designed as a non-inferiority trial (ISAR-Diabetes, single centre study with a surrogate endpoint). Based on the European Society of Cardiology established strict criteria with a clinical primary endpoint as a prerequisite to recommend a DES…A trial proving the superiority of one DES over another would require a multi-center study with a

clinical primary endpoint at an adequate power. As long as such a trial does not exist, Cypher and Taxus are regarded as being equivalent."

Potential Bias

Bias can occur in clinical studies from many sources and must be reduced in order to allow confident interpretation of the results. In some of the studies quoted by LRiG, important bias occurs due to several reasons, including:

- limited number of study sites (only 1 or 2 sites)
- questionable randomization schemes which may allow investigator bias
- unblinded angiographic assessments, and
- inadequate angiographic core laboratory (none used or lab is not independent of investigative site).

There is also a potential of bias due to mixed analysis types. In section 5.1.4 the authors focus on reported intent-to-treat results, but one study did not present ITT and in two studies, it is unclear which results are presented.

While small centre trials provide value to the clinical community by highlighting key patient groups and safety issues, these issues must be confirmed by large RCTs. Due to their smaller size and limits in design, *small centre trials are limited in the ability to make conclusions that are unsupported by a large RCT*.

Missing Reports from the Analysis

In its current form, the analysis is missing an important study designed to address this question in a 'real-world' setting. STENT (Strategic Transcatheter Evaluation of New Therapies) is the first multi-centre, prospective registry initiated to evaluate the long-term efficacy and safety of polymer paclitaxel- and sirolimus-eluting coronary stents among real-world patients and clinical situations. Baseline characteristics showed TAXUS stent procedures with slightly older patients, more ACS, slightly lower pre-procedure TIMI grade flow, slightly smaller vessel diameters and higher ACC lesion risk score. Even taking this into account, analysis of the initial ***3,758 patients*** of this 8,000 patient registry reported results favouring TAXUS over CYPHER at 9 months (TVR of 3.4% vs. 4.2% respectively)[10].

The AR references TSEARCH / RESEARCH, yet does not incorporate findings into its meta-analysis. In the study of high-risk patients, outcomes were contradictory, further highlighting the danger of basing decisions on conflicting evidence.

B. **Section 8:** ***Economic Evaluation: DES versus BMS***

Economic evaluation is generally limited by its applicability to a local setting. Therefore, the attempt by LRiG to convert efficacy to effectiveness, the 'holy grail' of economic evaluation, is laudable.

The attempt by LRiG to reflect NHS conditions through one centre has significant limitations – limitations that may incorrectly draw conclusions if adequate data is not available. In the specific case of the LRiG analysis, the results are misleading and incorrect due to:

- The inability to generalise CTC data to the whole of the NHS;
- The incorrect application of definitions for clinical endpoints;
- The methodology to calculate absolute risk reduction;
- The conflicting definition of risk factors;
- The large gap between the results and previously published literature.

Previous NICE guidance on the cost-effectiveness of DES applied known risk-factors of the disease state to evaluate benefit. This is the correct approach to this technology upon which new evidence should be built. We strongly urge NICE to return to its previous assessment approach which has proved effective and correct and to consider additional evidence for diabetics.

In addition, the relative risk reductions on page 135 comparing TAXUS and CYPHER DES are based on Section 5, which we find incorrect as argued above (A).

Generalisation of CTC Data to the NHS setting

The scope of this NICE review specifies the perspective of the NHS. Local variations in treatment practice, resource use, and outcomes may exist but a system-wide analysis should account for variations. There is yet no source to obtain effectiveness data for the NHS as a whole. Databases such as BCIS provide insight into uptake and possibly treatment patterns but do not provide any information on clinical effectiveness. Registries offer a partial solution as they should reflect real-world results, but they are viewed critically because they are not adequately controlled.

To overcome these limitations, the LRiG has proposed using its CTC database as a proxy for effectiveness of DES in the NHS. This is inaccurate and misleading as:

- Data from a single centre;
- Data source was audit data (non-DES treatment, non controlled);
- Data is collected over 2 years, however there is no specification as to how the data is collected or how treatment practice changed during that time;
- The authors apply DES trial results to local BMS patients, calling into question whether this is real 'effectiveness';
- The risk factors identified from audit data do not include those that are identified in the clinical literature, calling into question the patients / methodology;
- The risk factors call into question whether patients are subject to a selection bias;

If the CTC data is not applicable to the typical NHS treatment setting for PCI, the effectiveness data is not appropriate to perform an economic evaluation from an NHS setting. Therefore, efficacy data is the best clinical source available. There are numerous large multi-centre RCTs studying DES and registry results (the 'real-world') support their outcome. Possible variations in local treatment practice should be accounted for in a rigorous sensitivity analysis.

Incorrect Definitions for Clinical Endpoints

In Section 8.2.2, the authors present the definitions for clinical benefit of stents. The definitions of TLR and TVR are correct and these endpoints are reported by all large clinical trials. The third bullet point confusingly refers to further revascularisation due to disease progression, which DES cannot affect. The objective of DES is to reduce restenosis of a lesion (accounted for in TLR, TVR); they are not preventive measure against the progression of coronary artery disease (CAD). The NHS has a National Service Framework (NSF) in place addressing CAD, both in its prevention (e.g. education) and treatment. The use of PCI for treatment is in synergy with the goals set out in the NSF, not an alternative. Therefore, the application of this definition in the methodology is flawed – further discussion is found in the next section.

The last point in the section refers to increasing complexity of cases. The TAXUS clinical trial programme has been designed to account for increasing complexity of patients and lesions treated and to date has shown consistency in clinical results (please see Boston Scientific original submission for detail).

The authors also consider elective and non-elective PCI procedures. Further clarification is requested on the types of patients who are included in the definition of non-elective as acute myocardial infarction (AMI) falls outside of the current NICE scope and assessment.

Questions on Methodology

The authors introduce the method of applying efficacy data from trials to observational data from their centre in order to estimate effectiveness. Effectiveness is the measurement of device effect in a real-world setting (i.e. not ideal). The CTC database should include DES patients in order to measure effectiveness. The 'supposed' effectiveness based on efficacy is flawed; the entire analysis hinges on this supposition and is therefore detrimental to useful decision-making.

As mentioned in *Incorrect Definitions for Clinical Endpoints*, dilution of the treatment effect through a broader clinical endpoint of 'all revascularisations' (i.e. non-TVR) does not reflect the treatment objectives of DES. A correct approach is to consider DES within the setting of their intended effectiveness / efficacy (TVR or TLR). That the authors apply the risk reduction to 'all revascularisations', decreasing the expected treatment effect by half, is misleading and incorrect. To begin correction of the methodology, only patients with known TLR should be included and the 74.6% risk reduction applied to them.

The flaws in methodology are compounded in the calculation of absolute risk reduction due to DES (ARR), the basis of the cost-effectiveness results. Instead of the current approach, the 74.6% relative risk should be applied directly to the risk of repeat procedure.

Definition of Risk Factors

The previous NICE guidance, based on the clinical literature and its own review, identified patients with longer lesions (>15mm length) and small vessels (<3mm diameter) as being at increased risk of restenosis. There are several instances in this AR where the risk factors are called into question, using terms such as: "assumed" (page 13), "presumed" (page 133), and "belief" (page 61).

There is ample literature that highlights these sub-groups as at increased risk for restenosis, both in animal and human models. These factors have been identified before the advent of DES, as it is a factor of the disease itself. While diabetics tend to fall into one of these two risk groups, recent availability of large pooled patients has shown that diabetes is also a risk factor, independent of lesion length and vessel calibre.

We understand the motivation to evaluate risk factors in the CTC database, however it falls under the same limitations of a small RCT – the limited pool of patients. In the BCIA submission to NICE, large pools from registries (i.e. 'real-world' data) found small vessels, long lesions, and diabetes to be independent risk factors. In addition, the Boston Scientific submission to NICE detailed an internal analysis of pooled patient groups across trials which demonstrated these three factors as independent predictors of restenosis.

The NICE appraisal committee was previously correct in identifying patients with longer lesions and small vessel diameter as being at increased risk of restenosis and thus most likely to benefit from DES. As a result, we urge NICE to retain the recommendations for DES in patients with lesions >15mm in length or vessels <3mm in diameter. In addition, diabetes is an independent risk factor; hence the guidance should be extended to include diabetic patients who fall outside these anatomical criteria.

Results compared to the Literature

The original Boston Scientific submission included a review of the health economic literature related to DES; this is also reviewed in the AR. The LRiG analysis is clearly an outlier result when compared to international evaluations. A more recent publication in Sweden[11], added to the previously published literature, shows a clear benefit for high-risk patients. This is very much in line with the previous NICE guidance, with the addition of diabetics as an independent high-risk group. We ask NICE to review its previous assessment and return to this supported approach. As far as we are aware, no other piece of health economic analysis comes close to the LRiG's controversial conclusion.

C. **Differentiation of DES**

First, in Section 2.5.1, the authors refer to a grouping of data related to stents with similar drugs. We request that it be noted that there are two types of paclitaxel-eluting stents: those with a polymer and those without. Only TAXUS incorporates a polymer, while other paclitaxel-eluting stent systems do not. Throughout the AR, a reference is made to PES when referring to TAXUS results; we request that the definition is made explicit to prevent generalisation of TAXUS results across all PES systems.

In Section 5, the authors focus the DES vs. DES clinical discussion on the TAXUS and CYPHER stents. There is good quality clinical data in the form of the REALITY trial to support this discussion. Large RCTs such as REALITY have shown the feasibility of conducting a DES vs. DES trial and opened the debate for differentiation. For this reason, if a head-to-head trial does *not* exist between stents, it is no longer methodologically adequate to assume that other / newer stents are equivalent without an RCT to support this claim.

There is initial clinical evidence to support the differentiation of TAXUS and CYPHER DES from other DES. The ENDEAVOR III trial compared the ENDEAVOR® DES from Medtronic Corporation to the CYPHER DES. The trial missed its non-clinical primary endpoint and the higher 9-month TLR rate of 6.3% (ENDEAVOR) vs. 3.5% (CYPHER) indicates a possible clinical inferiority of the ENDEAVOR stent. As the AR suggests, further research is needed and until that time, TAXUS and CYPHER remain the only DES with adequate clinical data to support their use.

To note, a recent HTA published by DIMDI in Germany highlights the clinical differences expected from DES and groups the TAXUS and CYPHER stents separately from other DES as a result (www.egms.de).

On page 141, the authors state ***"It will be important therefore to evaluate comparative evidence of efficacy and safety for any future stent, and the benefits of one cannot be extrapolated to all."*** This is an appropriate statement and should be reflected in the final recommendations.

3. **Minor Comments**

- The report refers to Boston Scientific Ltd as "Boston" and should instead refer to the company as "Boston Scientific."

- ATLAS is incorrectly categorised as a non-controlled trial (page 38); it is a non-randomised controlled trial using a historical control.

- In Table 2-2, and on page xiv, eleven distinct DES designs are indicated. There are two TAXUS stents: TAXUS Express^{2TM} and TAXUS Liberté^{TM}. 'Liberté' is a bare-metal stent.

- A correction is required on page 34 in the discussion of stent thrombosis rates. There is a reference to two TAXUS trials (specifically TAXU II (SR) and TAXUS V) that are said to be at 2-years. In fact, the TAXUS V trial has not yet reached its 2-year time-point and there have been no reported increased stent thrombosis rates in the trial. We also ask that it be noted that the definition of stent thrombosis differs depending on the trial sponsor. The TAXUS clinical trial programme takes a very strict definition of stent thrombosis, reporting confirmed as well as presumed events.

- The AR recommends further comparison of DES to newer non-DES. The adoption of new alloy over stainless steel stents has been driven by improvements in deliverability not repeat revascularisation rates. The BASKET study, to which the report makes frequent reference, includes a newer BMS stent. The two DES used in the study show a statistically significant improvement versus this newer BMS, therefore it would seem to be an unsafe assumption that BMS technology will match the TLR improvements seen in DES.

- On page 142 the authors state "It is clear that given superior efficacy of …". As presented in this document, there is no conclusive data to support this claim – REALITY remains the only international large RCT comparing the two stents and it did not find evidence of superiority.

- On page 44, the authors claim that trials report exceptionally high revascularisation rates in the BMS arm ("typically up to 20-25%"). Clarification is requested as to which trials, what clinical measure is used, and at what time-point is being referred. A meta-analysis of the TAXUS clinical trial programme showed a 9-month TLR rate of 14.8% and TVR of 16.3%[12]. As the TAXUS programme is the single most comprehensive clinical programme in this field, the values cited by the authors cannot be 'typical.'

- Industry submission page 84. The CiC removed are TLR rate assumptions made for the sensitivity analysis. We request a clarification of this in the title to "Adjusted TLR rates used in sensitivity analysis."

- Section 2.3.2 discusses the results of a meta-analysis of CABG vs. PTCA. While CABG falls outside of the scope of this review, there are studies underway, such as SYNTAX, evaluating PTCA with DES vs. CABG.

- Page 11 addresses the clinical benefit of DES beyond 6-months. In the original Boston Scientific submission, data was presented demonstrating the durability of the effect to 2-years. Recent presentations at TCT 2005, Washington D.C. have shown an even longer durability of effect to 3-years. (Presentations of data available)

- On page *xv*, it is stated for the economic evaluation "it is assumed that all DES are clinically equivalent." This phrase is unsustainable. REALITY demonstrates clinical equivalence between TAXUS and CYPHER DES, but none of the other products under review have been subject to the same head-to-head trial.

4 Conclusions

The limitations of the primary data source used for this AR (the CTC database) has led to the AR reaching a number of obtuse conclusions that are at variance with the majority of evidence otherwise available both in the UK and world wide.

There remains only one large multi-national RCT comparing, head-to-head, the two major DES products currently available. This REALITY trial failed to reach its endpoint of superiority of one product over the other. This should be clearly stated in the AR and should be explicitly clear within any guidance issued.

The original NICE guidance on DES demonstrated cost-effectiveness of DES within a range of stated anatomical criteria. Subsequent CE studies in other countries have drawn similar conclusions. The AR based on CTC data is an absolute outlier in this regard, is flawed for the reasons shown above, and should not form the basis of revision to the original guidelines.

Diabetes has been shown in a number of studies to be an independent risk factor for restenosis and should be included in any revised guidance.

The above submission clearly shows performance differences between different DES products – they do not all fall into a single class of device. New entrants should be able to demonstrate clinical equivalence through comprehensive clinical trial programmes before being approved for use.

[1] Bagust A, Grayson AD, Palmer ND, Perry RA, Walley,T. Cost effectiveness of drug eluting coronary artery stenting in a UK setting: cost-utility study. *Heart* 2006 92:68-74.
[2] Thomas M. Are drug eluting stents really worth the money? *Heart* 2006;92:5-7.
[3] Doshi SN, Ludman PF, Towend JN, Buller NP. Estimated annual requirement for drug eluting stents in a large tertiary referral centre, according to new NICE criteria.. *Heart* May 2004, Vol 90, Supp.II, p A 41.
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April 2006

Dear,

Ischaemic Heart Disease – coronary artery stents – appraisal number 71

If there are any questions or clarifications needed, please do not hesitate to contact me either by e-mail or by telephone.

Yours sincerely,

Public Affairs Manager UK & Ireland
Boston Scientific Ltd

As all members of the Appraisal Committee are well aware, the work of NICE to date has set precedence for international HTA. It is the ability to objectively review evidence and make fact-based decisions that is appreciated by stakeholders, including patients and physicians, both in the UK and internationally.

Boston Scientific Ltd. (BSC) is a stakeholder with an appreciation for the NICE review process, as it normally offers a cooperative, transparent approach to assess the clinical value of a product. BSC is very proud of its clinical development programmes; trials are often developed in cooperation with physicians and have set new levels of quality in device RCT environment. The clinical trial programme centred on the TAXUS™ Stent is the largest of its kind and is innovative in seeking answers to those questions most on the mind of Interventional Cardiologists.

With this in mind:

- It is dismaying and disappointing to note that Addendum 3' lacks objectivity, transparency, and even quality of findings.
- The approach of the economic evaluation presented in the original TAR was fundamentally flawed and undeniably biased. The BSC response letter of January 2006 highlighted the major as well as some minor concerns in the analyses.
- The Addendum either does not address these issues at all, or addresses them within the biased, flawed framework of the TAR.
- An attempt to compare the Addendum to the request for further research from the Appraisal Committee found inconsistencies and heavy biases.

In the following pages, we have reiterated the 3 major objections to the approach taken by the LRiG:

1. Patients at increased risk of restenosis (Risk Factors and Sub Groups)
2. Appropriate measure of DES effectiveness
3. Best available data to apply effectiveness measure

We appeal to the Appraisal Committee to correct the biased approach taken by the Assessment Group in review of this Guidance.

1. RISK FACTORS AND SUB GROUPS

The previous Technology Appraisal for DES identified patients with small vessels (<3mm diameter) and longer lesions (>15mm length) as being at increased risk of restenosis. The previous TA and resulting Guidance were based on validated, robust data and should not now be discounted by limited data from a single centre.

The clinical evaluation of risk factors predates DES and is supported by numerous peer-reviewed publications. In the Addendum (page 33), the authors claim that the *perceptions of the genesis of restenosis may be misconceived*. To claim that the world of literature is misconceived based solely on the results from a small pool of patients from a single centre is a non-objective, self-serving comment by the Group.

Following the request by the Committee, the Group evaluated risk model factors in reviewed papers. ***It should be noted that small vessel has now been indicated as the strongest factor, and lesion length is a common factor. That these two risk factors had not previously been identified in the TAR puts the entire analysis into suspicion.*** It is an admission, though probably a reluctant one, by the LRiG that the previous Guidance correctly identified the risk factors and sub groups of interest.

What additional sources of information were reviewed by the Group in the Addendum? In its submission, BCIA included a table summarising the literature on predictors of restenosis. Of the 10 papers, 7 are based on clinical databases and not RCT. In the Addendum, the Group selected five papers and summarised risk model factors in Table A6.2. None of the papers selected by the Group identified diabetes; however a simple glance over the table submitted by BCIA (below) implies that diabetes is in fact an independent risk factor (7 of 10 papers).

We ask for the Committee's support in resolving this discrepancy. After the intervention of the Committee, the Appraisal Group has now validated small vessel and longer lesion as risk factors. As a result, the LRiG model has been shown to be inflexible and flawed.

With the wealth of data available in support of diabetes as a risk factor, the Group must consider all available sources in their evaluation and not 'cherry pick.'

Source	Univariate Predictors	Multivariate Predictors
Kastrati *et al* (1997). Factors predictive of TLR after stenting in ***routine clinical practice*** (n = 1,349).	Diabetes Multiple stents RVD <3.08mm Post-procedure MLD <3mm	Diabetes Multiple stents Post-procedure MLD <3mm
Singh *et al* (2005). Factors predictive of TVR in the PRESTO ***randomised trial*** of tranilast for the prevention of restenosis (n = 11,484)		Younger age Hypertension Diabetes mellitus Nonsmokers Unstable angina Previous CABG Peripheral vascular disease Ostial lesions Multilesion angioplasty LAD lesions Lesion length ≥ 20 mm In-stent restenosis Use of rotablator
Iakovou *et al* (2003) Factors predictive of TLR *in small vessels in* ***routine clinical practice***		In- stent lumen area ≤ $6mm^2$ Diabetes Absence of prior MI

(n = 423)		History of intervention
West *et al* (2004) Factors predictive of restenosis after stenting *in diabetic patients*. Meta-analysis of 16 ***randomised trials and registries*** (n = 3,090)	Lower BMI Smaller pre-procedure RVD Smaller pre-procedure MLD Longer stented length Smaller post-procedure RVD Smaller post-procedure MLD Larger post-procedure %DS	Lower BMI Smaller pre-procedure RVD Longer stented length
Kornowski *et al* (1999) Factors predictive of and repeat revascularisation *after multivessel stenting in* ***routine clinical practice*** (n = 2,339)		Unstable angina History of CABG History of PCI Diabetes Smaller reference vessel diameter
Nikolsky *et al* (2005) Factors predictive of TVR in patients who received bare metal stents in the TAXUS IV ***randomised trial*** (n = 1,307)		Longer stent length Smaller vessel diameter BMI ≥ 30kg/m^2
Jilaihawi *et al* (2005) Factors predictive of TLR in ***routine clinical practice*** (n = 1,112)		Diabetes
Bagust *et al* (2005) Cardiothroacic Centre (Liverpool) ***clinical database*** (n = 2,884)		*Elective patients* Calcification Angulation >45° Restenotic lesion Triple vessel disease *Non-elective patients* Vessel diameter <2mm Prior CABG
Wu *et al* (2004) Factors predictive of first revascularisation in registry of ***routine clinical practice*** (n = 3,571, 90% stented).		Multivessesl disease Stable vs. no angina Maximum stent length (longer) Diabetes (predictive of revasc by CABG only)
Agema *et al* (2004) Predictors of clinical restenosis (TVR) ***in routine practice*** pre-DES. (n = 3,177, 74% stented)		Diabetes Hypertension Peripheral vascular disease Mulitvessel disease C-type lesions

- Figure A3 is of little value due to small patient numbers – from the literature and the previous assessment, we know that large patient numbers are needed to show independence
- The previous point also applies to diabetes: in the previous assessment NICE commented that diabetes as a risk factor could not be shown with the patient numbers submitted. The CTC audit data has xx patients and would not be expected to have the sensitivity to detect this value.
- Boston Scientific has presented an analysis of pooled diabetes patients to demonstrate there is proof

2. DEFINITION OF DES EFFECTIVENESS

There are several excellent sources of information on the aetiology and progression of Coronary Artery Disease (CAD)[1]. Risk factors contributing to the development of CAD include diet, smoking, cholesterol, stress, and family history. CAD is a progressive disease – the disease process of atheroma leads to the development of symptoms (e.g. angina).

Treatment of CAD can either be preventative or symptom related, and there is a National Service Framework (NSF) addressing both. CABG and PTCA (with/without stent) address the symptoms due to atheroma; i.e. neither 'cures' CAD nor keep patients from returning for additional treatment due to disease progression. Instead, PTCA and CABG aim to reduce the stenoses in the target lesion(s).

According to the DFU, the TAXUS™ Stent System is indicated *for improving luminal diameter for the treatment of de novo lesions in native coronary arteries*. Drug-eluting stents do not propose to eliminate atheroma or affect the progression of CAD (neither does CABG). Studies of the **efficacy** of DES focus on relevant end-points such as TLR, TVR, or overall MACE. **Effectiveness** calculations should focus on assessing the same endpoints in an uncontrolled setting. The LRiG propose instead to evaluate DES based on **all revascularisations**; e.g. treatment for a newly-formed stenosis in a new vessel. Applying the same logic to laser treatment for glaucoma, the treatment would be considered ineffective if first used in the right eye of a diabetic patient who, due to the morbidity of disease, later develops glaucoma in the left eye.

The glaucoma example should sound ridiculous – if it does not, this is an essential 'stop' to product development and evaluation and the implications are devastating.

Although the BSC response letter of January 2006 addresses the methodological flaws of the approach in greater detail, the Addendum has ignored all comments. We appeal to the Committee to correct the inaccurate, legally challengeable definition and approach used by the Group.

3. BEST AVAILABLE DATA

The BSC response letter of January 2006 contains discussion on grading of evidence and the generalisation of the CTC Data to the NHS setting. ***The NICE 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 Scottish Registry. Instead, the Group has taken a mix of sources and ***adjusted the values to fit to the CTC dataset.***

We appeal to the Committee to correct the manipulation of the data and ask the LRiG to instead return and consider the BASKET trial and RCT evidence reviewed in the first half of the TAR.

Observational data has an important role in considering the effectiveness of medical devices. Well constructed, high-quality observational studies offer an alternative to RCTs, ***depending on what questions are being asked***. The TAR contains a major disassociation due to completely different sources of evidence considered for the first section, the clinical evaluation, versus the second, the economic evaluation. 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.

In Section 1.2 of the Addendum, the suitability of observational studies/ audit data was considered. None of these sources contain data that is relevant to the evaluation of DES: they offer some interesting data, but to ascertain the cost-effectiveness of DES, the RCTs remain the only valid source of evidence. Limitations of non-RCT studies of observational / audit data:

- Do not support the hierarchy of evidence or standards of Evidence Based Medicine
- No consistency
- Do not capture evidence of DES impact (most are from a pre-DES era and therefore subject to question of validity of using data and extrapolating results)
- Include a high proportion of STEMI patients
- **Are manipulated to reflect repeat intervention rates based on flawed CTC database**

Boston Scientific is committed to the development of robust clinical trial programmes to support the use of DES. With the approach taken by LRiG, we question the usefulness of continued investment into these programmes.

Disutility Values

The Appraisal Committee requested that the Assessment Group consider possible disutility of post-CABG for 6 weeks. The work presented in the Addendum instead considers a 'plausible' state of minimum utility for 2 weeks and a gradually increasing utility for another 2 weeks (4 weeks in total). As a stakeholder in this process, we ask for clarification:

- Why was a decision made to focus on 4 weeks and not 6 weeks as the Committee requested? i.e. who made the decision that this is instead 'plausible' and based on what evidence?
- Why was the utility level of PCI also hypothesised to be lower for 2 weeks?
- Looking at the slope of the 2 lines in Figure A.1, is it plausible that the utility values for post-CABG patients will increase at a steeper rate than that for PCI patients? Source?

Other Points Demonstrating Negative Bias of Assessment

- Although the Appraisal Committee asked for stent wastage rates of 1% and 5%, Assessment Group considered instead 1% and 10%
- Due to addendum work, an inadvertent mistake was found in the CTC audit data (large number of STEMI patients had been included). This raises a question on the quality of this database – has someone validated it? We raised this question in our response letter of January 2006 – have the other points been checked for as well?
- In Table A6.3, the example given takes assumptions on the higher end, intending to exaggerate the ICER results (5% instead of 1% wastage, Cypher instead of Taxus)
- On page 18, wording 'suspicion that DES could lead to loss of life expectancy." The Group earlier push for evidence based claims, and then give a biased opinion with no evidence base.

[1] Selection of sources on CAD/CHD: www.bhf.org.uk, www.bupa.co.uk, www.prodigy.nhs.uk