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Dear Emily,

Ischaemic Heart Disease – coronary artery stents – appraisal number 71

Please find a response from Boston Scientific to NICETAR 04/42 as requested. For the sake of brevity we have responded specifically to the above-referenced document but would request that this response is considered in conjunction with our original submission to the guideline review (27 June 2006) and our response to the Liverpool Review Group Assessment Report (12 January 2006.)

Yours sincerely,

Public Affairs Manager UK & Ireland
Boston Scientific Ltd

Contents:

1. Executive Summary

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 and economic 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 the device RCT environment. The clinical trial programme centred on the TAXUS™ stent is the largest and most comprehensive of its kind.

Bearing the above in mind it is disappointing to see that Addendum 3 continues in the vein of the original TAR i.e. flawed findings of questionable quality based on demonstrably inadequate data.

The conclusions presented by the LRiG regarding the cost effectiveness of drug eluting stents are based overwhelmingly on their analysis of the patient database at the Cardio-Thoracic Centre in Liverpool, using their own model to conduct this analysis. This model is fatally flawed and conflicts with conclusions and data from widespread clinical trials - as such the conclusions drawn from it cannot be viewed as being robust.

The original guidance established by NICE in September 2003 proved to be a major contributor to the achievement of the NSF targets on revascularisation 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 surprising were NICE to issue guidelines based on the LRiG approach which would make the NHS an absolute outlier in terms of this technology.

In section 4 we add to the current evidence on diabetics in the form of a soon to be published meta-analysis by Keith Dawkins et al demonstrating the benefit of the TAXUS™ DES in the diabetic population. This is in addition to the evidence previously presented and reviewed in Section 3c, demonstrating diabetes to be an independent risk factor. We request that the new NICE guidelines reflect this evidence.

2. The LRiG Model

In Addendum 3 the LRiG continue to use their model as the basis for their conclusions. This of course contains the same inherent problems as were seen in the first report namely:

- single centre data
- non-randomised data
- self-selected patient group
- patient numbers not powered to show results of independent risk factors
- risk factors identified that are inconsistent with weight of international clinical evidence
- lack of consistent follow-up
- data possibly not well-coded (e.g. inclusion of STEMI patients in the TAR assessment)

Using this data LRiG came up with a series of conclusions that were contrary to the initial NICE guidelines and all other published data in this field. When asked to conduct further analysis by the Committee, LRiG, by their own admission state:
'In the case of the CTC audit data, we noted that a number of AMI patients had been inadvertently included in the non-elective group. These were removed and the revascularisation rates re-estimated - the changes from this modification are minor' (P26:52)
This begs the question of how much else within the database and therefore the model is erroneous and makes it wholly unreliable for the purposes of conducting this assessment.

In the original TAR the LRiG discounted vessel size and lesion length as independent risk factors yet in Addendum 3 they recognise these as significant factors. This casts further doubt on the credence of their entire approach.

LRiG then attempt to force the data to fit their conclusions and make the following statement:
'There is no standard method of reporting outcomes, and therefore it is necessary to attempt to adjust authors' chosen measures into a comparable standard, compatible with our economic model. This has involved employing additional evidence and assumptions, which in some cases are not as rigorously derived as we would have liked.' (P26:52)

There is no transparency in their method thus once again rendering any conclusions from their analysis untenable.

In the discussion of Procedural Disutility (P14:52) LRiG have produced a graph based on a series of assumptions that they have made – there is no validation for their assumptions whatsoever. On the contrary, multiple sources have indicated that CABG patients suffer far greater disutility. The drastic reduction in mean disutility per patient for PCI patients results in a much greater cost-effectiveness ratio than indicated in the paper. *(reference to STS patient info and Scottish Coronary Heart Disease Task Force report.)*

There are numerous other examples of the inherent weaknesses in the Assessment Group's report due to the fundamental flaws in the base data and model. These are shown in section 6 – Addendum of this document.

We ask the Committee to review the current LRiG model and consider reverting to the model used in previous assessment of DES, which has no reason to be questioned.

2. Major comments to LRiG Addendum

A 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 interpretation and approach used by the LRiG.

B 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 the flawed CTC database**

Boston Scientific is committed to the development of robust clinical trial programmes to support the use of DES and other medical technologies. The approach taken by LRiG in this instance appears to be contrary to the principles of evidence-based medicine which we seek to support.

C 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 surprising claim that is unsubstantiated within the document.

Following the request by the Committee, the LRiG 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.

The LRiG do not make it clear which additional sources of information were reviewed by them in Addendum 3. In its submission, BCIA included a table summarising the literature on predictors of restenosis. Of the 10 papers, seven 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. The table submitted by BCIA supports diabetes as an independent risk factor (7 of 10 papers). Curiously, there are seven papers that were not chosen by the LRiG – five of those demonstrate that diabetes is an independent risk factor for repeat revascularisation.

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 LRiG must consider all available sources in their evaluation and not selectively include those which appear (when adjusted) to support their conclusions.

Although, two of the papers selected by the Group identified diabetes, the LRiG found reason to discount both: the Netherlands paper because a $p>0.1$ was set as the removal criterion for a backwards stepwise regression, and the Washington State paper because diabetes was predictive of repeat revascularisation by CABG. As far as we are aware, in current statistics a $p>0.1$ is a standard cut-off point for a backwards stepwise regression, and a repeat revascularisation with CABG is still a repeat revascularisation. We ask that the Group reverse its decision to exclude the two papers on these weak grounds.

Drug-eluting stents (DES) have been shown to be much more effective compared to bare metal stents (BMS) in reducing target lesion revascularization (TLR). The National Institute for Clinical Excellence (NICE) provides guidance on the use of

DES for patients with small vessels and long lesions, but excludes diabetic patients, arguing that diabetes is no longer an independent risk factor for TLR once *vessel size* and *lesion length* are considered in the risk adjustment model, due to the multicollinearity among diabetes and these two lesion characteristics. Using the pooled data from 2 randomized controlled trials of paclitaxel-eluting Express stent with slow release (SR) formulation (TAXUS IV and V trials), we are able to show that diabetes is a significant risk factor for TLR after adjusting for lesion length, vessel diameter in a multiple logistic regression model. A significant benefit in TLR reduction through 9 months was confirmed for paclitaxel DES versus BMS in patients with or without diabetes.

4. New Data: Diabetes

An integrated analysis of patients from the TAXUS trials has investigated the benefit seen in diabetic patients vs. non-diabetics when treated with BMS vs. DES. Results are conclusive and robust in support of the benefit of TAXUS stenting in this high-risk sub-group.

Please note that patients from two of these trials (moderate-release trials excluded) were pooled in an internal analysis demonstrating diabetes as an independent risk factor (see Section 3c above). This analysis was submitted to NICE last year.

NB Please find with this response the paper from Dawkins et al that has been accepted for publication in *EuroIntervention.*

5. Conclusions

The original NICE guidelines in September 2003 were based on a wealth of clinical and economic evidence. Since these guidelines the evidence base has increased demonstrating sustained benefit from DES technology and showing this technology to be cost effective for high-risk patient sub-groups (small vessels, long lesions). In addition we have presented data that shows diabetes to be an independent risk factor and cost-effective to treat using DES.

The original guidelines have contributed to the NHS increasing revascularisation rates in a cost-effective manner, helped reduce waiting lists and given thousands of patients improved outcomes.

The approach taken by NICE has been viewed in many parts of the world as being balanced and evidence-based.

The evidence presented by the LRiG, and their subsequent analysis of this evidence, does not measure up beside the weight of clinical evidence provided by RCTs and multi-centre trials. In fact the LRiG conclusions fly in the face of this evidence and contradict the evidence-based beliefs of the international cardiology community.

It would be an opportunity lost on a grand scale were the NHS to throw away the gains of the last few years that this technology has brought and revert to higher volumes of more costly surgery, increased waiting times due to lack of infrastructure and increased length of stay on the back of a flawed report based on single centre data that has been demonstrated by a number of sources to be wholly unreliable.

An endorsement of the current guidelines, with the addition of diabetes as an independent risk factor, would match the available and reliable evidence that we have and would bolster the NHS in sustaining the improvements already made in the treatment of CHD.

6. Addendum – minor points in response to Addendum 3

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?

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%
- 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."* This appears to be wholly speculative and as such of no value in this guideline development process.

A Note on DES vs. DES

- Although the Addendum did not address the issue of DES vs. DES, several tables reported results of the TAXUS and Cypher stents independently
- As reviewed in on our submission as well as the response of January 2006, there is no conclusive data to support differentiation of a single DES
- Only the TAXUS and Cypher stents have robust clinical trial programmes of greater than three years follow-up, and their results cannot be extrapolated to all DES (as stated in the TAR)
- REALITY, an RCT comparing the TAXUS and Cypher stents failed to meet its primary endpoint
- Recent publications of head-to-head studies in patient subgroups at high risk of restenosis demonstrate a trend in favour of the TAXUS Stent
- Without supporting high-quality ***data in those sub-groups that fall within possible NICE recommendation for use***, superiority of a single DES cannot be made

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