From: [redacted] [redacted]
Sent: 29 August 2007 16:37
To: Reetan Patel
Cc: [redacted]
Subject: Boston Scientific response to ACD for TA 71 - August 2007

Attachments: Boston Scientific ACD ResponseFinal.doc; CiC removed; BCIA Response to DES ACD v2.doc

Dear Reetan,

Please find enclosed the Boston Scientific response to the ACD.

CiC removed.

- the BCIA response that Boston Scientific fully supports.

If you need additional information, please do not hesitate to give Mark McIntyre or myself a call,

Best regards,

[redacted]

[redacted]

Health Economics & Public Affairs

Boston Scientific UK & Ireland

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29 August 2007

Dear Reetan,

Ischaemic Heart Disease – coronary artery stents – appraisal number 71
Appraisal Consultation Document– August 2007

Please find the response from Boston Scientific to the ACD for TA71. Please also note that Boston Scientific will be a contributor to the BCIA response which is also attached.

If you have any queries regarding this communication please contact me via e-mail at [redacted] or by telephone on [redacted].

Yours sincerely,

[redacted]
Boston Scientific Ltd

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Introductory Comments

Section 1 will describe the failure to follow the appraisal methodology set out on the Institute's *Guide to the Technology Appraisal Process*

Section 2 will highlight the highly selective approach used by the Committee to reach its conclusions on cost-effectiveness and look in detail at the parameters used in the economic analysis

Section 3 will draw attention to the Liverpool Assessment Group's conflict of interest and why this group is an inappropriate one to conduct this review

Section 4 will examine the likely impact that this draft guidance would have from the following perspectives:

i. patient care and patient choice
ii. commissioners
iii. providers

Conclusions

Additional issues

Introductory Comments

Boston Scientific fundamentally disagrees with the draft guidance contained within the ACD for TA71 and the basis upon which this has been prepared.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.

1. Failure to follow the appraisal methodology set out on the Institute's *Guide to the Technology Appraisal Process*

1.1 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.****"*

1.2 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.."*

Element of health technology assessment	Reference case	Section providing details
Defining the decision problem	The scope developed by the Institute	5.3.2
Comparator	Alternative therapies routinely used in the NHS	5.3.2
Perspective on costs	NHS and PSS	5.3.3
Perspective on outcomes	All health effects on individuals	5.3.3
Type of economic evaluation	Cost-effectiveness analysis	5.3.4
Synthesis of evidence on outcomes	Based on a systematic review	5.4.1
Measure of health benefits	Quality-adjusted life years (QALYs)	5.5
Description of health states for calculation of QALYs	Health states described using a standardised and validated generic instrument	5.5
Method of preference elicitation for health state valuation	Choice-based method, for example, time trade-off, standard gamble (not rating scale)	5.5
Source of preference data	Representative sample of the public	5.5
Discount rate	An annual rate of 3.5% on both costs and health effects	5.7.2
Equity position	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	5.9.7

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 and non-RCT evidence can be used. However the potential selection bias should be assessed in an analysis of uncertainty.

1.3 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 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."[1]

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.

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 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.

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:

   - 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 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.

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[2] 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 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.

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 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

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

See	Parameter	Figure	Source
2.1	BMS absolute risk of revascularization general population	11%	BASKET? + Scottish Registry?
2.2	BMS absolute risk of revascularization Small vessels	19%	BASKET corrected by risk factors from CTC database
2.2	BMS absolute risk of revascularization Long lesions	11.7%	BASKET corrected by risk factors from CTC database
	Mean number of stents	1.571	CTC database
2.3	DES relative risk reduction	55%	Expert opinion based on BCIS literature review
2.3	DES relative risk reduction subgroups	n/a	n/a
2.4	Price premium	£600	2004/05 NHS PASA survey

We explain below our continuing concerns in relation to the assumptions adopted by the Appraisal Committee for the purposes of the ACD:

2.1 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 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 publication reporting the 11% revascularization rate for BMS. Our research found the 18-month follow-up reported in the European Heart Journal in 2007[3]. 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.

2.2 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 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.

2.3 Relative risk reduction with DES

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 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.[4] 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.

2.4 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 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.

[redacted]

CiC table removed.

[redacted]

3. Bias from the Assessment Group

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*[2]), this has been comprehensively challenged by Dr Martyn Thomas[5], 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 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.

4. Overall impact on the NHS and on patient care

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 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).*"[6] (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 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'.

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.

Additional Issues

Please find specific comments related to sections of the ACD:

4.1.10 For TLR, the meta-analyses showed statistically significant differences in favour 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

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).*"

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.

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 additional costs for the use of this stent should be based on 6 months, not 9 months.

[redacted]

References

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

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