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12th January, 2006.

Dear Ms. Fuller,

Response to Assessment Report: Coronary Artery Stents for the Treatment of Ischaemic Heart Disease (Update to Guidance No. 71).

Thank you for the opportunity to respond to the above Assessment Report (AR). This is a difficult report to respond to in a concise yet constructive manner, to productively inform the Committee's discussion. Cordis have four general areas of concern and several points specifically in connection with the Assessment Group's critique of our economic model. The general points are:

1. ***A conflict of interest within the Assessment Group.*** The AR follows controversial opinions expressed in the previously published paper by Bagust *et al* (2005). Such a firmly held view of the relative value of drug eluting stents (DES) made it unlikely that the AR would present an impartial review of all the submitted evidence.
2. ***The derivation of DES effectiveness that underpins the economic evaluation.*** The AR unreasonably minimises the risk reduction attributable to DES by expressing the avoidance of repeat revascularisations in terms of 'all revascularisations' rather than target lesion or target vessel revascularisation rates. Furthermore, the methodology employed is not transparent.
3. ***The identification of patients who are at high risk of repeat revascularisation following stenting and the size of that high-risk population.*** The AR dismisses patients with longer lesions, small vessels and diabetes as representing high-risk groups most likely to benefit from DES, in favour of factors identified from a single hospital database. In fact, longer lesions, small vessels and diabetes are restenosis risk factors that have been widely and repeatedly validated in the literature. The AR thus underestimates both the absolute risk of repeat revascularisation and the size of the population at risk.
4. ***Use of generic DES treatment effect in the economic model.*** Meta analysis of the Cypher versus Taxus trials presented in the AR demonstrated a significant treatment effect in favour of Cypher (odds ratio 0.68 [95% CI 0.51 to 0.91]). Despite this, the economic model assumed no difference in effectiveness between the two devices but employed differential costs.

The underestimate of the absolute risk of repeat revascularisation associated with bare metal stents (BMS) and the underestimate of the risk reduction attributable to DES results in an erroneous conclusion that DES are cost-effective in only a small proportion of the population.

Three of the general concerns above have been also been raised in the British Cardiovascular Industry Association response, but are restated here to emphasise their importance.

Conflict of Interest

Three months prior to the deadline for submission to this Review, a paper was published (Bagust *et al*, 2005) that included amongst its authors, two key members of the Assessment Group responsible for this AR. These people were Professor Bagust (who developed the economic model) and Professor Walley (responsible for interpreting the clinical and economic data). This publication is the basis of the economic evaluation in the AR, yet there is no explicit declaration of an overlap in authorship and it is not mentioned in the "declaration of interests" at the beginning of the AR. Quite remarkably, the authors undertook a review of their own publication and needless to say, pronounced it to be of the highest quality.

The conflict of interest centres on the fact that some members of the Assessment Group entered the Review with a pre-formed, published opinion on the cost-effectiveness of DES. They have a vested interest in a piece of primary research that is at the extreme of the wider published literature. This calls into question their ability to undertake an impartial assessment of all of the published and submitted evidence – the principle that should underpin an Assessment Report. At best they should hold commentator status with respect to this Review. Though Assessment Groups may not have commercial links to technologies, such strongly held pre-formed opinions as those reported in the Bagust paper, must be viewed as a potential source of bias when the group comes to undertake what should be an independent AR. This conflict of interest was raised with the Institute & DoH in May, through the industry groups. In our view, academic conflicts of interest should be treated in the same manner as commercial conflicts of interest: potential for academic advancement and direct economic benefit should be viewed in the same light. .

The Derivation of DES Effectiveness Used in the AR

This pertains to the ***risk reduction*** attributed to DES in the AR. The risk reduction is unreasonably minimised in the AR, leading to over-estimation of the ICERs in the economic model

The purpose of a DES is to reduce the rate of repeat revascularisation associated with restenosis of BMS. DES are not intended to reduce the need for other procedures in non-stented segments of the same artery or other arteries due to disease progression. Thus, there is a need to differentiate between **repeat revascularisation** due to restenosis (which can be reduced by DES) and **further revascularisation** due to disease progression, which cannot be reduced by DES. There is a general acceptance amongst clinical experts that the most accurate way to measure the treatment effect of DES is to compare rates of target lesion revascularisation (TLR), i.e. the rates of repeat revascularisation due to restenosis within the stent (+ 5mm either side). By way of a hypothetical example, **repeat TLR** rates of 50/1000 (5%) for DES and 150/1000 (15%) for BMS equate to a reduction in TLR of 75% (100 out of 150 TLR events avoided). If further revascularisations due to disease progression (assumed to be 30 events in each arm) are now counted, the 'all revascularisation' rates (repeat + further) become 80/1000 (8%) for DES and 180/1000 (18%) for BMS. However, the reduction in 'all revascularisations' is only 56%, because DES have avoided the same 100 procedures, but out of a total of 180 procedures, not 150 (same absolute reduction but applied to a higher baseline).

In section 8.2 of the AR, an adjustment in treatment effects is outlined under the heading "Converting efficacy into effectiveness". It is not clearly stated, either mathematically or functionally, how the relative risks quoted in this section are derived from the DES treatment effects correctly

quoted as odds ratios Chapter 4. The adjustment appears to allow a relative risk (RR) for the reduction in all revascularisations to be derived from the RR for the reduction in TLR obtained from the trials. In one of the AR scenarios, the relative risk reduction (RRR) in TLR of (74.6%, RR=0.25) estimated from the trials is applied to 'all revascularisations' seen in the CTC audit. The overall RRR for all revascularisations is then 50.5%. In this scenario although it is true that the RR for all revascularisations is less than the RR for TLR (as the baseline rate is greater), the absolute reduction in all revascularisations and RR for TLR are unaltered.

In the second AR scenario, the RRR of 74.6% percent (RR=0.25) in TLR is applied only to those cases where only the target lesion was revascularised in the CTC audit. The RRR is then 38% for all revascularisations. This would adjustment would only be valid if:

1. We believed that those patients who had both a target lesion and non-target lesion revascularisation would still have had a non-target lesion revascularisation if the target lesion had not been revascularisation. This assumption is invalidated in the AR by the comment (page 95) *"It is not possible to determine whether or not the repeat procedures could have been avoided by use of DES in these cases, as we cannot identify which lesion(s) was the primary source of recurrent symptoms in these patients."*

2. Both target and non-target lesion revascularisations occur at the same time and there is no extra cost and reduction in quality of life associated with the TLR over the non-TLR.

Neither of these assumptions is robust and it is therefore misleading for the AR to state (page 95) that: *"Half (51%) of patients receiving a second intervention required repeat treatment only to previously treated lesions; these are the patients in whom DES can be expected to produce benefit"*. DES will produce benefit in **all** patients at risk of a TLR.

The AR also states on page 95 *"However, it is clear that only between a half and two-thirds of the reported DES benefit (in terms of reduced TLR) can be expected to result in reduced numbers of patients presenting for repeat revascularisation within 12 months."* The benefit in absolute reduction in TLR should only be discounted only if there is no extra costs and disbenefits for those patients who also have a second revascularisation and then only by approximately 30%

In summary, the Assessment Group acknowledges on page 135 of the AR that their approach may be considered extreme. The 'all revascularisations' approach unreasonably minimises the treatment effect attributable to DES. Modelling cost-effectiveness based on all revascularisations should at the very least include the costs and utility effects of all subsequent revascularisations, but the Assessment Group have not done this. Rather, they have tried to adjust the relative treatment effect in a non-transparent way that has led to an overestimation of the ICERs for DES

Identification of Patients at High Risk of Repeat Revascularisation and the Size of the High-Risk Population.

This pertains to the ***absolute risk*** of repeat revascularisation in BMS, the ***characteristics*** of patients who are at increased risk and the ***proportion*** of patients in those groups. By relying upon a single hospital database, the AR has ignored predictors of repeat revascularisation that have been validated repeatedly and consistently in multiple studies over the past decade, underestimated the absolute risk associated with BMS and underestimated the proportion of patients at risk.

The original Technology Appraisal of DES correctly identified patients with longer lesions (>15mm length) and small vessels (<3mm diameter) as being at increased risk of restenosis and the resulting Guidance recommended that patients meeting these 'anatomical' criteria should receive either a Cypher or Taxus DES. The AR creates a perception that longer lesions, small vessels and the presence of diabetes do not predispose patients to a high risk of restenosis, rather that these factors are "assumed" (page 13) or "presumed" (page 133) to define those at risk or represent a "belief" (page 61). The language implies that these risk factors are founded in folklore rather than clinical science. This representation is grossly misleading, is based largely on the findings presented in the Bagust paper (itself relying on data from a single hospital) and makes only brief reference to the wealth of other published data. **Fundamentally, long lesions, small vessels and diabetes probably fail to feature in the Liverpool risk model because they do not reach statistical significance in that model, not because they are not predictive.**

The original submission to this Review by the British Cardiovascular Industry Association (BCIA) presented the results from 10 studies that sought to identify factors predictive of repeat revascularisation in patients who received BMS, 7 of them based on 'real world' clinical databases, not randomised trials. The purpose of this was to confirm that the original Guidance was still consistent with data that may have been published since it was issued. BCIA adopted an approach of using all available evidence (including the Bagust paper). The result was that 6 studies identified smaller vessel diameter or a related measure of smaller in-stent area or smaller lumen diameter post procedure as being an independent predictor of restenosis or repeat revascularisation (all except one identified the clinical, not the angiographic outcome). Five studies identified longer stent/lesion length and 7 studies reported diabetes as an independent risk factor. Thus, the AR and the Bagust paper should be seen in context – they contribute to the dataset, but when all the evidence is considered, the Appraisal Committee was correct when it previously identified ***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, Cordis believes that the current recommendations for DES in patients with lesions >15mm in length or vessels <3mm in diameter should be retained. In addition, diabetes is an independent risk factor; hence the guidance should be extended to include diabetic patients who fall outside these anatomical criteria.

The AR asserts that only when the risk of repeat revascularisation with BMS reaches 16-18% (page 120), do DES become cost-effective and these rates are only reached when 2 or more 'Liverpool' risk factors are present. However, the requirement for 2 or more risk factors relies on the assumption that the 'Liverpool' risk factors are correct. This assumption is unreliable as the wider literature shows that longer lesions, small vessels and diabetes are more widely validated risk factors. The AR also makes much of revascularisations driven by the follow up angiograms mandated by trial protocols. This was recognised as an issue in the BCIA submission, so an overview of all studies that did not include trial protocol-driven revascularisations was presented. This analysis included the Bagust publication, recognising that it had something to contribute to the overall result and does not select the single publication that best represents DES. The biggest single contributor to the review, the PRESTO trial, with 36% weighting, is not even referenced in the AR.

The results of the BCIA analysis, repeated below for convenience, demonstrate that the underlying risk in all patients is between 11-12%. Table 7-4 (page 81) of the AR shows that the trial-based TLR/TVR rates used in the general populations in the Boston Scientific, Cordis and Medtronic economic models are in the range of 12.8-15.5%, within the range shown below. This demonstrates that the clinically-driven TLR/TVR rates seen in the DES randomised trials are not greatly different from the range of data seen in the literature where there is no protocol-mandated angiographic follow-up. Thus, any remaining effect of the angiogram in the clinically-driven trial repeat revascularisation rates is very small. Accepting that the rates in high-risk patients will, by definition,

be greater than in unselected patients, it is clear that patients with longer lesions, small vessels and diabetes have an ***absolute risk*** (excluding protocol-driven revascularisations) in the range that makes DES cost-effective.

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	9.1%
Shrive *et al*, 2005	7,334	601	8.2%	12m any revasc, clinical database	23.2%
Singh *et al*, 2005	11,484	1,609	14.0%	PRESTO trial. 9m TVR, ischaemia-related revasc	36.4%
Jilaihawi *et al*, 2005	1,003	51	5.1%	12m TLR, clinical database	3.2%
Serruys *et al*, 1998	206	16	7.8%	BENESTENT II trial. 12m TLR no angio group	0.7%
Kalzula *et al*, 2004	38	6	15.8%	ELUTES trial control group. 12m TLR symptom driven revasc	0.1%
Stone *et al*, 2004	385	49	12.8%	TAXUS IV trial control group. 12m TLR no angio cohort	1.2%
Holmes *et al*, 2004	525	85	16.2%	SIRIUS trial control group. 12m TLR angina driven revasc	1.7%
Lemos *et al*, 2004	380	41	10.9%	12m TVR angina driven, clinical database	1.2%
Serruys *et al*, 2001	600	102	21.0%	ARTS trial stent arm. 12m all revascs, no follow-up angio	1.9%
Wu *et al*, 2004	3,571	577	16.2%	12m revasc, prospective registry of routine practice	11.3%
Agema *et al*, 2004	3,177	304	9.6%	9m TVR in routine clinical practice	10.1%
Overall	**31,587**	**3,721**	**11.8%**		**100.0%**

Table 1. Reproduction of Table 3 from the original BCIA submission. *Summary of evidence for repeat revascularisation risk in a mixed population of patients treated with bare metal stents, excluding the effect of protocol-mandated angiographic follow-up. 'Weight' shows the percentage each study 'N' contributes to the overall 'N'. Clinical databases contribute 58.1% of the overall population. The 8.8% shown for Bagust et al represents the overall revascularisation rate in the complete CTC population.*

The cost-effectiveness results presented in the AR are critically dependent upon the acceptance of the single-centre Liverpool data which, as noted above, are an outlier in terms of both the absolute risk of repeat revascularisation and the identification of high-risk groups. The AR points to another UK database (Jilaihawi *et al*, 2005) in support of its claim that BMS repeat revascularisation rates are low in unselected patients. However, the AR fails to report that the same study found, in contradistinction to the AR and the Bagust paper, that diabetes was a predictor of repeat revascularisation. The reliability of the AR comes into question as data appear to have been used selectively to support the pre-formed opinions expressed in the Bagust paper.

The AR suggests that DES have been over-used in the NHS - more than the 30% suggested in the original Guidance (page 145) - and that clinicians will find any change to this "unpalatable". In response, the Committee should note that when consultation took place on the ACD and FAD during the original appraisal of DES, it was reported by many stakeholders that the figure of 30% under-represented the patients in the target groups, even though the 30% figure remained in the published Guidance. In fact, it is the case that the original Guidance under-estimated the true population size, rather than that DES have been over-used relative to that Guidance.

Finally, it is of value to look in more detail at the impact of the angiogram on Cordis' cost-effectiveness modelling. The AR notes that the FDA definition of a clinically-driven repeat revascularisation includes procedures performed on the basis of *"an in-lesion diameter stenosis >70% in the absence of ischaemic signs and symptoms.."*. The AR then goes on to state that *"Even by this definition,*

clinically-driven events can be based on angiographic indices alone". Since the original submission, Cordis have had the opportunity to undertake further analysis of the patient-level trial data and to remove any repeat revascularisation based on the '70% stenosis' criterion that was ***not*** accompanied by ischaemic signs and symptoms. In other words, the model has been re-run based on only repeat revascularisations driven by clinical ischaemic signs and symptoms. The results for the 2-way (Cypher versus BMS) model are shown in Table 2 below, alongside the originally submitted results that were based on the FDA criteria of clinically-driven revascularisations. Table 3 shows a similar analysis for the 3-way model. The conclusion of Cypher's cost-effectiveness in these groups remains unchanged, putting 'to bed' any lingering doubts about the direct use of trial results in the economic model.

Risk Factor	ICER using clinically-driven revascularisations	ICER using revascularisations driven by ischaemic signs and symptoms
No risk factors	£29,259	£30,712
Small vessels	£10,178	£9,070
Long lesions	£16,460	£17,942
Diabetics	£9,702	£13,800

Table 2. Comparison of Cypher versus BMS ICERs derived by using the internationally accepted definition of clinically-driven repeat revascularisations and ICERs derived by using ischaemia-driven revascularisation (i.e. with the 'angiogram effect' excluded from the patient level data). *The conclusion of the cost-effectiveness of Cypher versus BMS remains unchanged providing the NHS is willing to pay up to £17,942 per QALY gained.*

Risk Factor	Device	ICER using clinically-driven revascularisations	ICER using revascularisations driven by ischaemic signs and symptoms
No risk factors	BMS Taxus Cypher	 Extended dominance £34,066	 Extended dominance £34,063
Small vessels	BMS Taxus Cypher	 Extended dominance £11,736	 Extended dominance £11,740
Long lesions	BMS Taxus Cypher	 Extended dominance £16,460	 Extended dominance £21,214
Diabetics	BMS Cypher Taxus	 £11,925 Dominated	 £11,930 Dominated

Table 3. Comparison of Cypher versus BMS versu Taxus ICERs derived by using the internationally accepted definition of clinically-driven repeat revascularisations and ICERs derived by using ischaemia-driven revascularisation (i.e. with the 'angiogram effect' excluded from the patient level data). *The conclusion of the cost-effectiveness of Cypher versus BMS and Taxus remains unchanged providing the NHS is willing to pay up to £21,214 per QALY gained.*

Use of Generic DES Treatment Effect in the AR Economic Model.

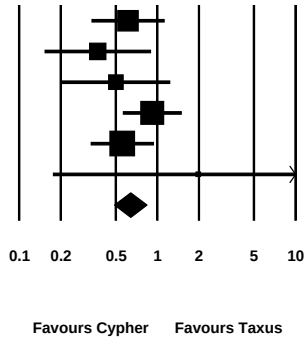
Meta analysis of the Cypher versus Taxus randomised trials presented in the AR demonstrated a significant treatment effect in favour of Cypher (odds ratio 0.68 [95% CI 0.51 to 0.91]). This result is very similar to the undisputed reduction in repeat PCI gained by BMS over balloon angioplasty without stents in occluded vessels (odds ratio 0.64 [95% CI 0.42 to 0.93]) (Brophy *et al*, 2003). Despite this, the AR economic model assumed no difference in effectiveness between Cypher and

Taxus whilst including differential costs. This is perverse. If differential costs are used for Cypher and Taxus, then differential effects should be used as well. Page 135 acknowledges that there is a 33% relative risk reduction for Cypher versus Taxus, and it is insufficient, as the AR proposes, to make post-hoc adjustments to the overall result to estimate an ICER for each device.

The difference between Cypher and Taxus has been demonstrated in the publication by Kastrati *et al* (2005), which also included the ISAR-DESIRE trial. This study reported an odds ratio in favour Cypher of 0.64 (95% CI 0.49 to 0.84, P = 0.01) and the results are reproduced below for convenience. It is important that the differential effects of Cypher and Taxus are recognised because in the AR analysis, the number needed (NNT) to treat is 47 (95% CI 27 to 178) and in the Kastrati analysis, 38 (95% CI 24 to 96). The potential for benefit from such a low NNT is very tangible when, if current growth rates continue, 83,000 PCIs could be performed in the UK in 2006. Indeed, the difference in economic value between Cypher and Taxus has recently led to the Italian Health Ministry to assign Cypher a higher reimbursement price than Taxus (www.ptca.org/nv/desnews.html).

Meta-analysis: Cypher versus Taxus Randomised Trials

Model	Study name	Outcome	Statistics for each study						MH odds ratio and 95% CI
			MH odds ratio	Lower limit	Upper limit	p-Value	Cypher	Taxus	
	CORPAL	TLR	0.613	0.336	1.117	0.110	19 / 331	29 / 321	
	ISAR DESIRE	TLR	0.371	0.154	0.892	0.027	8 / 100	19 / 100	
	ISAR DIABETES	TLR	0.501	0.205	1.229	0.131	8 / 125	15 / 125	
	REALITY	TLR	0.920	0.568	1.488	0.733	34 / 684	36 / 669	
	SIRTAX	TLR	0.557	0.332	0.935	0.027	24 / 503	42 / 509	
	TAXI	TLR	1.980	0.177	22.189	0.580	2 / 102	1 / 100	
Fixed			0.642	0.491	0.841	0.001			



Test for heterogeneity: Q = 5.802, df = 5, P = 0.41, I-squared = 1.61%

Figure 1. Reproduction of the meta-analysis of Cypher versus Taxus randomised trials published by Kastrati et al (2005). *'Fixed' = results using a fixed effects model.*

In addition to these general issues, we wish to respond to the following criticisms of the Cordis model:

- Description of competing alternatives and choice of year 2 discounting rates.
- Methodology of the Cypher versus Taxus versus BMS modelling.
- The utility values used and the impact of waiting times with symptoms.
- Price of DES, and differential with BMS.

Description of Competing Alternatives and Choice of Year 2 Discounting Rates

The AR comments on page 85 that the competing alternatives examined in the Cordis economic evaluation were not stated. Section 5.1 (page 31) of our submission states that we employed both a

2-way model of Cypher versus BMS and a 3-way model of Cypher versus Taxus versus BMS. One assumes therefore that since 'BMS' was clearly stated as a comparator, the Assessment Group are noting that the specific brand names of the BMS comparators (e.g. Bx VELOCITY™ Coronary Stent) were not identified. We would point out that the Assessment Group's also uses the term 'BMS', not brand names, for the comparator in their model.

With regard to discounting rates used in year 2 of our model, the AR comments that we have used 3.5% for both costs and outcomes not 6% for costs and 1.5% for outcomes. This point, like the description of alternatives, is minor and pedantic. The 3.5% discounting rate is recognised and recommended in the Institute's Reference Case, as is our probabilistic modelling approach (which was not followed by the Assessment Group).

Methodology of the Cypher versus Taxus versus BMS Modelling

The Assessment Group reject the 3-way analysis undertaken in the Cordis submission on the grounds that different BMS were used in the Cypher versus BMS trials (Bx VELOCITY stent) and Taxus versus BMS trials (EXPRESS and NIR stents). This, they argue, relies on the assumption that different BMS are equivalent – an assumption that may not be valid because of potential differences in outcomes between 'thick strut' and 'thin strut' stents. The 3-way model is thus considered in the AR to be subject to "serious concerns" on the grounds of the impact of "non-random heterogeneity between studies". Three comments on this:

1. The Assessment Group's economic evaluation is predicated on the same assumption because patients of CTC Liverpool who constitute their BMS comparator will have been treated with more than one type of BMS with different strut thicknesses. UK hospitals usually stock more than one type of stent so that the most suitable device can be chosen for each case.
2. The 'thick strut' versus 'thin strut' debate is not as the AR states. Firstly, strut thickness is a continuous variable when all types of stent are considered – there is no defined dimension that separates 'thick' from 'thin' so such categorisation is meaningless. Secondly the statement *"thick strut BMS such as Bx VELOCITY are inferior to thin strut BMS such as EXPRESS"* is misleading – the Bx VELOCITY and EXPRESS have not been compared in randomised trials. Thirdly, newer alloy stents that tend towards the thinner end of the range of strut thickness have been adopted on the basis of improved deliverability, not lower revascularisation rates. The patient and lesion-related factors are infinitely greater determinants of restenosis rates than what BMS is used. In fact, as a recent elegant review clearly demonstrates (Mauri et al, 2005), there may as much as a 4-fold difference in the TLR rate seen with any given BMS, depending on patient and lesion-related characteristics. It seems extraordinary that the Assessment Group are so wedded to the notion of "thick" versus "thin" stents, which is highly controversial, and reject the patient and lesion-related determinants of restenosis, which are well established.
3. The Assessment Group has not understood the 3-way model. This model does not rely solely on the BMS control arms of the Cypher versus BMS and Taxus versus BMS trials to derive the treatment effect of Cypher versus Taxus. All the available Cypher versus Taxus randomised trials have also been included, and the overall 3-way evidence synthesis that informed the economic evaluation was implemented using a Bayesian hierarchical logistic model. The use of an unconstrained baseline means that treatment effect estimates were affected only by differences *within* trials and not differences between trials. This methodology has been presented both orally and as a poster at two recent international meetings (Hawkins and Sculpher 2005a, 2005b).

The Utility Values Used and the Impact of Waiting Times with Symptoms

The utilities used in the Assessment Group model are more favourable to Cypher than those used by Cordis, whereas the waiting times used by Assessment Group are less favourable to Cypher. Table 4 below shows the impact of using the Assessment Group's utility values and waiting times in the Cordis 2-way model of Cypher versus BMS. Implementing these values does not change the overall conclusion of cost-effectiveness.

Scenario	ICER using Original Cordis Model	ICER using Assessment Group Utilities and Waiting Times
No risk factors	**£29,259**	**£38,814**
Small vessels	**£10,178**	**£13,493**
Long lesions	**£16,460**	**£21,894**
Diabetics	**£9,702**	**£12,901**

Table 4. Impact of Assessment Group utility values and waiting times on the cost-effectiveness of Cypher in the Cordis economic model. *The conclusion of cost-effectiveness does not change.*

Price of DES, and Differential with BMS.

The price issue is not straight forward, and raises a number of issues unique to devices that the Institute does not face with pharmaceuticals. Pharmaceutical prices tend to be reasonably constant over time during the period a drug has patent protection, and decrease only when generic competition is possible. Devices, on the other hand, do not benefit from long periods of market exclusivity. It is easier for a competitor to develop an alternative device to do the same job than it is for a drug company to find a new compound, and once the idea is in the public domain, the time to market is relatively short, compared with drugs. This results in much earlier competition, a shorter product life cycle, and greater market price competition. Average selling prices therefore fall more quickly than with drugs. The AR over-simplifies the market conditions for stents, and reports on a lack of competition for DES. This view we suggest is misguided, and a wider understanding of the market conditions is required to inform the review.

When BMS were the novel technology, introduced in the mid-1990s, the list price was of the first BMS to market (produced by Johnson & Johnson) was approximately £1,500. The first DES (Cypher, Johnson & Johnson) was introduced in 2002 again with a list price of £1,500, in real terms lower than the original BMS list price. In 1998-99, the mean market price for BMS in five UK hospitals was £698 (range £750 to £500) (Sculpher *et al*, 2002). At the time of the first stent HTA in 2000 (TA number 4), Meads *et al* (2000) reported list prices for BMS ranging from £650 to £1,440 (table 58) and average selling price appeared to be around £500 (table 55). The stent review in 2002 (TA no. 71) reported a cost for BMS of £341 whilst Jenkins *et al* (2002) reported a cost of £380 in the same year, giving an average of £361. The current AR reports a market average of £278. Thus, market prices of BMS (the comparator for DES) always fall within a wide range, but overall, have fallen dramatically over time. This introduces real problems when market prices are used as a comparator for DES. These price changes are summarised in Figure 2.

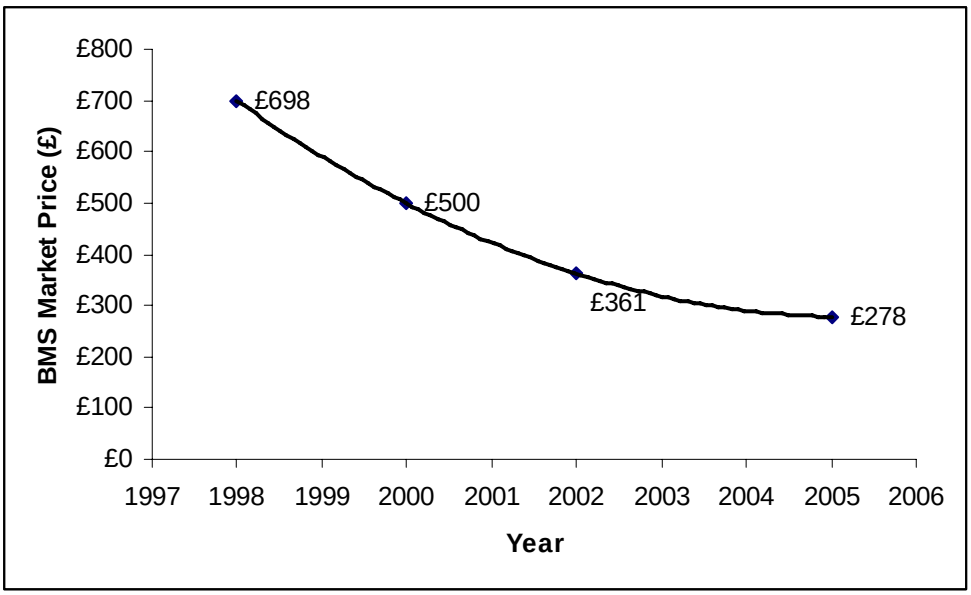


Figure 2. **Variation of average BMS market prices over time.** *Technology appraisals were conducted in 2000 and 2002.*

As DES usage has spread to >50% of all stent usage since the 2003 guidance, suppliers of BMS have been left chasing a smaller market. To retain a market presence, price competition ensued, and so BMS prices have dropped rapidly leaving the BMS market increasingly commoditised as a result of the availability of DES. As new entrants join the DES market, price competition can expect to depress the ASP of DES over time.

It should be noted that the newer, cheaper DES are gaining access to the market with less supporting evidence. Hence the AR quote "*Cordis have shown a reluctance to deviate substantially from a narrow price range*" is because Cordis needs to recoup the investment made in the extensive clinical development programme required to be first to market before cheaper 'generics' remove the value from this innovation and drive it towards a BMS-type commodity market.

With specific reference to the statement "*The cost data for the technologies (both BMS and Taxus) appear implausible. Both the costs of Taxus and the BMS were substantially overestimated…*" (page 85), list prices were used throughout in the Cordis model as the recognised practice for Technology Appraisals. This is in line with the position paper submitted by ABHI during 2005, and the use of list prices was agreed at the original scoping meeting.

Thus, the debate around price centres on:

- The current low market price of BMS is an artifact of the availability of DES. If DES were not available, the BMS price would not now be so low. Since DES became available, the demand for BMS has fallen. The principles of supply and demand dictate that if demand falls but supply remains, the price will fall.
- The price paradox - if the BMS price continues to fall, DES may not model as cost-effective at that future price. Yet if DES had not been originally recommended for use in the NHS, the price of BMS would be higher, so DES would remain cost-effective. At the same time, the real value of DES to patients in terms of relief of their symptoms remains undiminished. What therefore is the appropriate comparison? The methodology becomes unreliable in this case when repeated reviews are undertaken. If this line of reasoning is pursued to its logical conclusion,

there would potentially be regression to the least expensive therapy even if it had already been rendered obsolete.

Other minor comments

- The AR comments on *"….the limited supply of Cypher stents…".* We wish to clarify that Cypher supplies have only been temporarily interrupted and this was a voluntary measure to ensure that only the highest quality product reached UK patients. We would also point out that Cordis are not the only DES manufacturer to have suffered supply interruptions. If the Assessment Report is to include this sort of comment, it should report all situations pertaining to all manufacturers and be clear about the reasons.

Summary

- A conflict of interest within the Assessment Group has led to a failure to consider all of the available evidence and a failure of impartiality.
- The ***under-estimation of the absolute risk*** of repeat revascularisation with BMS, the ***under-estimation of the risk reduction*** to be gained from DES and ***incorrect identification of at-risk groups*** have led to an inaccurate assessment of the cost-effectiveness of DES.

We appreciate the opportunity to respond to this Assessment Report. We hope the Committee recognises the issues raised in this response and our desire to ensure that the Review should take a balanced and reasonable course. We stand by our original submission in full, and believe that drug-eluting stents represent a clinically and cost-effective intervention for NHS patients. We are happy to try and provide any additional details requested on the points raised above where required.

Yours sincerely,

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References

Agema WR, Monraats PS, Zwinderman AH, De Winter RJ, Tio RA, Doevendans PA, Waltenberger J, De Maat MP, Frants RR, Atsma DE, Van Der Laarse A, Van Der Wall EE, Jukema JW (2004). Current PTCA practice and clinical outcomes in The Netherlands: the real world in the pre-drug-eluting stent era. *Eur Heart J* 25(13):1163-1170.

Bagust A, Grayson AD, Palmer ND, Perry RA, Walley T (2005). Cost-effectiveness of drug-eluting coronary artery stenting in a UK setting: cost-utility study. *Heart* Apr 14; [Epub ahead of print]. http://heart.bmjjournals.com/cgi/content/abstract/hrt.2004.053850v1.

Brophy JM, Belisle P, Joseph L (2003). Evidence for use of coronary stents. A hierarchical bayesian meta-analysis. *Ann Intern Med.* May 20;138(10):777-786.

Hawkins N, Sculpher M (2005a). The cost-effectiveness of drug-eluting stents based on a synthesis of the results of 15 randomised controlled trials. ISPOR 8th Annual European Congress, 6–8 November 2005, Florence, Italy, Abstract IC1.

Hawkins N, Sculpher M (2005b). Evaluating the cost-effectiveness of drug-eluting coronary stents: the results of a Bayesian evidence synthesis and decision model. Society of Medical Decision Making http://smdm.confex.com/smdm/2005ca/techprogram/P2364.HTM.

Holmes DR, Leon MB, Moses, MD JW, Popma JJ, Cutlip D, Fitzgerald PJ, Brown C, Fischell T, Wong SC, Midei M, Snead D, Kuntz RE (2004). Analysis of 1-year clinical outcomes in the SIRIUS trial: a randomized trial of a sirolimus-eluting stent versus a standard stent in patients at high risk for coronary restenosis. *Circulation* 109:634-640.

Jenkins NP, Prendergast BD, Thomas M (2002). Drug eluting coronary stents. *BMJ* Dec 7;325(7376):1315-1316.

Jilaihawi H, Khan S, Kovac J (2005). Low incidence of revascularisation of bare stents in the era of drug-eluting stents: a single tertiary centre experience. *Heart* 91 (Suppl 1):A5.

Kastrati A, Dibra A, Eberle S, Mehilli J, Suarez de Lezo J, Goy JJ, Ulm K, Schomig A (2005). Sirolimus-eluting stents vs paclitaxel-eluting stents in patients with coronary artery disease: meta-analysis of randomized trials. *JAMA.* Aug 17;294(7):819-825.

Kaluza GL, Gershlick AH, Park SJ, De Scheerder I, Chevalier B, Camenzind E, Goy JJ, Missault L, Reifart N, Vrints C, Urban P, Shim WH, Ho DS, Fearnot NE, Voorhees WD 3rd, Raizner AE (2004). Comparison of neointimal formation in polymer-free paclitaxel stents versus stainless stents (from the ASPECT and ELUTES randomized clinical trials). *Am J Cardiol* Jul 15;94(2):199-201.

Lemos PA, Serruys PW, van Domburg RT, Saia F, Arampatzis CA, Hoye A, Degertekin M, Tanabe K, Daemen J, Liu TK, McFadden E, Sianos G, Hofma SH, Smits PC, van der Giessen WJ, de Feyter PJ (2004). Unrestricted utilization of sirolimus-eluting stents compared with conventional bare stent implantation in the "real world": the Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) registry. Circulation Jan 20;109(2):190-195.

Mauri L, Orav EJ, Candia SC, Cutlip DE, Kuntz RE (2005). Robustness of late lumen loss in discriminating drug-eluting stents across variable observational and randomized trials. *Circulation* Nov 1;112(18):2833-2839.

Meads C, Cummins C, Jolly K, Stevens A, Burls A, Hyde C (2000). Coronary artery stents in the treatment of ischaemic heart disease:a rapid and systermatic review *Health Technol Assess.* 4(23):1-153.

Sculpher M, Smith D, Clayton T, Henderson R, Buxton M, Pocock S, Chamberlain D (2002). Coronary angioplasty versus medical therapy for angina. Health service costs based on the second Randomized Intervention Treatment of Angina (RITA-2) trial. *Eur Heart J.* Aug;23(16):1291-1300.

Serruys PW, Unger F, Sousa JE, Jatene A, Bonnier HJRM, Schönberger JPAM, Buller N, Bonser R, van den Brand MJB, van Herwerden LA, Morel MAM, van Hout BA (2001). Comparison of coronary artery bypass surgery and stenting for the treatment of multivessel disease. *N Eng J Med* 344(15):1117-1124.

Serruys PW, van Hout B, Bonnier H, Legrand V, Garcia E, Macaya C, Sousa E, van der Giessen W, Colombo A, Seabra-Gomes R, Kiemeneij F, Ruygrok P, Ormiston J, Emanuelsson H, Fajadet J, Haude M, Klugmann S, Morel MA (1998). Randomised comparison of implantation of heparin-coated stents with balloon angioplasty in selected patients with coronary artery disease (Benestent II). *Lancet* Aug 29;352(9129):673-81

Shrive FM, Manns BJ, Galbraith PD, Knudtson ML, Ghali WA (2005). Economic evaluation of sirolimus-eluting stents. *Canadian Medical Association Journal* 172(3):345-351.

Singh M, Gersh BJ, McClelland RL, Ho KK, Willerson JT, Penny WF, Holmes DR Jr (2005). Predictive factors for ischemic target vessel revascularisation in the Prevention of Restenosis with Tranilast and its Outcomes (PRESTO) trial. *J Am Coll Cardiol.* 45(2):198-203.

Stone GW, Ellis SG, Cox DA, Hermiller J, O'Shaughnessy C, Mann JT, Turco M, Caputo R, Bergin P, Greenberg J, Popma JJ, Russell ME (2004). One-year clinical results with the slow-release, polymer-based, paclitaxel-eluting TAXUS stent: the TAXUS-IV trial. *Circulation* 109:1942-1947.

Wu AH, Goss JR, Maynard C, Stewart DK, Zhao XQ (2004). Predictors of repeat revascularisation after nonemergent, first percutaneous coronary intervention in the community. *Am Heart J* 147(1):146-150.