Ms. C Fuller,
Technology Appraisals Manager,
National Institute for Clinical Excellence,
MidCity Place,
71 High Holborn,
London
WC1V 6NA.

12th January, 2006.

Dear Ms. Fuller,

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

Thank you for the opportunity to comment on the assessment report (AR) on drug eluting stents (DES). Medtronic would like to take this opportunity to address their concerns under three main headings:

1. Conflict of Interest
2. Clinical data interpretation
3. Economics
    - Critique of manufacturer economic submissions
    - Liverpool economic evaluation of DES vs. BMS

In summary Medtronic believes that the clinical data interpretation is not representative of the evidence base and that this misinterpretation has led to unfavourable conclusions on the cost-effectiveness of DES.

1. Conflict of Interest

On 7th June 2005 Medtronic wrote to Professor Sir Michael Rawlins to express concern regarding the believed conflict of interest of the Liverpool assessment group. As outlined, two members of the assessment group (Professor Bagust and Professor Walley) published an article prior to the deadline for submission to this review which concluded that the technology could not be considered cost effective.

Whilst we understand that academic health economists want to publish their research, there is a conflict when the same individuals wish also to act as the authors of independent reports used in the health technology assessment arena. We do not believe that members of the Liverpool group can be impartial under these circumstances, indeed, it is perverse that Professors Bagust and Walley were responsible for critiquing their own publication to assess its quality, less perverse is that is that they scored their own work highly. At the very least a clear declaration of potential conflict should be included.

When the clinical and economic findings of the Bagust and Walley paper are compared with other published literature on DES it is clear that their conclusions are not reflective of the general literature. It is therefore of particular concern that this publication, taken in isolation, has clearly been used as the basis for the economic evaluation described in the AR. As stakeholders we strongly believe that we have entered a process where the assessment group had preconceived views on the clinical and cost-effectiveness of DES and that this has introduced clear bias into the process. The fairness of this appraisal must therefore be called into question otherwise the integrity of the NICE appraisal process and the Institute may be damaged.

2. Clinical data interpretation

- ***Efficacy vs. Effectiveness***

The AR states in on a number of occasions (e.g. pages 31, 33, 44) that "there is no further added value of DES after the first year". The same argument has been used to justify the one-year time horizon of the economic model.

The basis of this statement/opinion is the assessment group's use of 'all revascularisations' as their preferred outcome measure, despite target lesion revascularisation (TLR) risk reduction being the standard measure. The justification given for this approach is the assessment group's unsound opinion that TLR risk reduction represents a measure of 'efficacy', whilst 'all revascularisation' risk reduction represents effectiveness. This approach is perverse and clinically irrelevant. DES are designed to reduce the rate of repeat revascularisation that would have occurred due to restenosis within a bare metal stent (BMS) had a BMS been implanted. How, therefore, can taking account of further revascularisations in unstented segments required due to disease progression be attributable the effectiveness of initial DES stent placement? This flawed approach, (in part acknowledged in the AR, page 135) in essence dilutes the treatment effect of DES directly, and wrongly affects the results of the assessment group's cost-effectiveness model.

Using the appropriate clinical outcome of TLR risk reduction the stability of the odds ratios over time shows that DES maintain their advantage over BMS for up to 3 years (and possibly longer) i.e. DES keep leading to lower revascularisation rates and therefore further cost savings over time. On this sound clinical basis a longer time horizon should have been chosen for the model.

Example:

Using data on TLR from the SIRIUS trial as reported in the Appendix of the assessment report (figure 3), DES continue to have lower number of new TLRs over time, leading to the stability of the ORs (see Table 1) . If the number of new TLRs with DES were the same as with BMS after the first year, the ORs would have to be increasing with time, as shown in Table 2.

Table 1 Actual observations

	DES			**BMS**			**OR**
n	533			525			
Time	# of cases	New cases	% of new cases	# of cases	New cases	% of new cases	
6-9 mths	22	22	4.13%	87	87	16.57%	**0.22**
2 years	34	12	2.25%	112	25	4.76%	**0.25**
3 years	36	2	0.38%	122	10	1.90%	**0.24**

Table 2 Assume no benefit of DES after one year

	DES			**BMS**			**OR**
n	533			525			
Time	Assumed # of cases	Assumed new cases	% of new cases	# of cases	New cases	% of new cases	
6-9 mths	22	22	4.13%	87	87	16.57%	**0.22**
2 years	***47***	***25***	***4.76%***	112	25	4.76%	**0.36**
3 years	***58***	***10***	***1.90%***	122	10	1.90%	**0.40**

- ***Identification of high risk patients***

Current NICE guidance on DES recommends lesion length (>15mm) and vessel diameter (<3mm) as the anatomical criteria indicating high risk of restenosis and thus determining whether patients should receive a DES. We believe that data published since the last appraisal supports this approach, however, the current AR infers that lesion length and diameter no longer indicates that patients are at a high risk of restenosis (pages 13 and 33 of AR). Again, it is clear that the findings from the Bagust and Walley publication have influenced this change in opinion with the assessment group choosing to ignore alternative/independent published data which supports NICE's original guidance in favour of the authors own single centre data. Such data biases are not acceptable in an evidence based review and must be corrected to allow fair economic evaluation.

- ***Omission of relevant risk factors***

We believe that current literature supports diabetes as a clear 'stand alone' risk factor for restenosis and that guidance should be extended to include diabetic patients as a discrete high risk group suitable for treatment with DES

- ***Exclusion of dosage studies of single DES types***

The AR (page 19) defines DES type based solely on the type of drug eluted. The report also acknowledges that type of delivery, catheter, and a number of other factors may also influence results. Medtronic would like to point out that drug dose has been omitted as 'a factor' and should be included to facilitate usage of all useful data sources.

- ***Inferences on data quality***

Page 22 of the AR states "The absence of complete datasets, suitably detailed reports and presentation of aggregate data, limited the depth of assessment of the manufacturer submissions". Medtronic believes that its reporting of the ENDEAVOR trial in its submission was comprehensive and of high quality with the original trial reports being sent to the Institute for use by the assessment group in their analysis. Medtronic therefore find it perverse that the data provided gave enough information for inclusion in the meta-analysis but was not included in the economic evaluation. Clarification of the rationale for this decision would be appreciated.

- ***Transparency of data selection/reporting***

The table presented on page 23 of the AR lists 37 studies, but only 25 RCTs were included in the meta-analyses (and even less used in the economic evaluation). It is not clear why 12 studies were excluded, clarification on this would be appreciated. Additionally, the section on DES vs BMS 17 RCTs are mentioned, but the tables in the Appendix show data for only 16 RCTs.

3. Economics

Critique of manufacturer economic submissions

- ***General methodological issues***

On page 77 of the AR the two five-year timeframe model scenarios presented by Medtronic are described as one in which the reduction of the risk of repeat vascularisations with DES was assumed to last until the end of the first year, and another, in which reduction of risk was extended beyond the first year and for the remaining period of analysis. It is then stated that "The data however only supported the first scenario, as trial data are only available up to nine months". This statement goes against the whole rationale for the need and conduct of economic modeling (refer to Halpern MT, Luce BR, Brown RE et al. Health and economics outcomes modelling practices: a suggested framework. Value in Health 1998;1:131-47). The exact reason why modelling is needed is to extrapolate results beyond the trial time horizon and explore different alternatives, otherwise a simple trial-based cost-effectiveness analysis would have be sufficient.

- ***TLR/TVR rate parameter values from industry submissions***

On page 81 of the assessment report TLR/TVR rates used in industry submissions are presented. Due to the AR authors reliance on data contained in their publication it is important to note that the TLR/TVR rates for BMS in the Bagust model are much lower than those used in any of the industry submissions.

- ***Critical appraisal of Medtronic model***

On page 87 of the AR it is stated that the second scenario of Medtronic's model is inappropriate: "Firstly, it is based on the results of a meta-analysis of studies covering only the first year of analysis". This statement is made despite the meta-analysis performed in the clinical section showing that the ORs remain stable over time (up to three years). There needs to be greater consistency between messages in the clinical and economic sections.

The AR goes on to state that "Secondly, the meta-analysis from which the odds ratio was taken used only evidence for Taxus and Cypher, and not Endeavor". When Endeavor trial data is studied it is clear that Endeavor showed similar reductions in TLR and TVR to the other DES at nine months. Modelling includes the use of assumptions and Medtronic believes that the assumption of similarity in odds ratios is valid. As Medtronic acknowledges that this data is assumption based the model developers tested the assumption in line with good practice, the results showed that the reductions to be observed at longer time horizons will also be similar.

The critique goes on to state that "TLR and TVR rates are not equivalent". Medtronic would like to state that whilst TLR data was used to approximate for TVR, it was not the rates that were assumed to be equivalent, but the reductions in revascularisations as measured by ORs. Whilst Medtronic acknowledge that this may be a strong assumption, we believe it had to be made because TVR ORs were not available from the meta-analysis used.

With respect to the statement regarding "MACE odds ratios for DES … had been used mistakenly in place of TLR odds ratios" we would like to apologise for this error. However, we would also like to point out that the OR mistakenly used was 0.42 (0.32 to 0.53) instead of the true TLR OR of 0.26 (0.14 to 0.45). Therefore the analysis used a less favourable assumption towards Endeavour than what the actual meta-analysis data would have suggested.

At the end of the first paragraph on page 87 the AR states that "… the extrapolation of outcomes to five years as performed in the Medtronic economic model submission seems implausible." Based on the arguments already stated Medtronic do not believe the extrapolation was implausible. Furthermore, the base case model presented assumed no difference between the two stents after the first year, and the extrapolation criticised here was presented only as an alternative scenario. Therefore, stating that the extrapolation performed in the Medtronic economic model is not accurate is an unfair representation of our submission.

With respect to resource use data the AR states that "The stent resource usage … was derived from a trial population …and likely to be selective". All effectiveness data was based on trial data. It would have been even more implausible to base TVR, MACE, etc. rates on the trial but the number of stents leading to these event rates on other data sources.

Liverpool economic evaluation of DES vs. BMS

- ***Other events***

On page 92 of the AR it states: "However, the estimated benefit … appears to be stable over the long-term, suggesting that all or the great majority of benefit accrues within the first 12 months". This is the same error discussed in the clinical section critique (section 2). Additionally the statement is illogical, if the authors are to wrongly purport that potentially all the benefit were to accrue in the first year, then estimated benefit would have to decrease over time.

- ***Converting efficacy to effectiveness***

Whilst this point has already been covered to a degree in the clinical section critique (section 2), the content of section 8.2 of the AR again raises the question of what is under investigation in this appraisal? The treatment of the target lesion or the treatment of CVD? Liverpool excluded from the model events that were thought to be unrelated to DES or not differentially affected by DES (e.g. MIs), therefore to be consistent with this approach, they should have omitted "unrelated" revascularisation events from the model instead of reducing effectiveness.

- ***Effectiveness estimates from observational data***

Crucially, effectiveness estimates used in the Liverpool model are predominantly generated from the single centre patient sample from Liverpool CTC. As previously stated, this data is not consistent with other published literature with respect to baseline risk of repeat revascularisation and the identification of high risk groups and must therefore be considered an outlier. The assessment group's use of the Jilaihawi *et al*, 2005 UK database paper to 'selectively' justify their use of CTC data for effectiveness measures is erroneous. How can an 'impartial' technology assessment group use Jilaihawi to support the CTC data used to show that BMS revascularisation rates are low in the general population, but omit to point out that the same study, contrary to the CTC data, shows diabetes to be a predictor of repeat revascularisation?

Additionally, the authors of the AR are selective in which data they use. With respect to lesions treated in repeat revascularisations, in the calculation of benefit, the authors here exclude CABG cases, even though CABG is valid option to treat lesions requiring repeat revascularisation.

- ***Economic assessment methods***

The models pivotal part is the application of an absolute risk reduction due to DES defined as the risk of repeat procedure with BMS (based on the Liverpool data) multiplied by the relative risk reduction due to DES (based on the meta-analysis results adjusted for 'effectiveness'). This approach is valid for the type of patients in the clinical trials included in the meta-analysis (i.e. the first result column in Table 8-8). However, it is likely that the examined subgroups differ not only in their baseline risk of repeat revascularisation with BMS, but that DES have a differential efficacy in the patient subgroups. Additionally, the Liverpool 'risk factors' used cannot be assumed to be correct, indeed, the wider independent literature shows that the risk factors of longer lesion and smaller diameter (as used in the original appraisal) are more valid.

- ***Costs included***

On page 107, clopidogrel therapy has been omitted from the analysis with the reasoning that it accrues "no incremental cost". This is true for the index procedure, but not for repeat procedures. If DES are effective in reducing the need for repeat procedures, they also reduce the need for lengthy and costly clopidogrel therapy. Therefore its omission biases the model against DES, by the exact cost amount of the number of repeat procedures saved times the cost of 12 months of clopidogrel treatment. The current model also omits any other treatment related to repeat revascularisations that were included in the previous HTA report: e.g. rehabilitation, which is also a cost for the NHS. This further biases the results against DES.

- ***Parameter values and data sources for Liverpool model***

On Page 113, Table 8-7 it is unclear which relative risk reduction was used to derive the absolute RR. The meta-analysis reports ORs for both TLRs and TVRs. The 'efficacy adjustment' is also reported based on three different approaches.

- ***Analyses and results***

The aim of the report was to assess DES against BMS. The comparison with BMS is complete only for Taxus and Cypher, but there is no mention of the other DES, although the relevant trials were included in the clinical sections.

- ***Budget impact assessment***

The BIA is too simplistic, taking into account only the projected number of procedures per year and the incremental costs of DES over BMS. It does not take into account the fact that DES reduce the number of repeat revascularisations.

Summary

In summary, Medtronic is disappointed, but not unsurprised with the quality and content of this assessment report given the publication history of the assessment group and the clear conflict of interest inherent in their data selection. The presentation of the clinical and cost-effectiveness of DES is unbalanced and perverse; it does not represent current clinical opinion and could potentially lead to guidance be generated which is not relevant to the NHS and therefore not implementable.

If an unbiased presentation of the data was made, using all evidence available (including that published since the original appraisal) the natural conclusion to be reached would be for the original recommendations to stand i.e. DES recommended for patients with lesions >15mm in length or vessels <3mm in diameter. In addition, diabetes as a 'stand alone' risk factor should be added to ensure the needs of all high risk patients is met.

Medtronic would like to recommend, in the interests of fairness, that another assessment group without a conflict of interest reviews the current AR. There is a potential need for another assessment report to be prepared which presents a clinically balanced and valid interpretation of the evidence on DES.

Please do not hesitate to contact me if you need any further clarification or information from Medtronic.

Yours sincerely,

Principal, Health Economics and Market Access
Medtronic Ltd