Reetan Patel,
Technology Appraisal Project Manager,
The National Institute for Health and Clinical Excellence,
MidCity Place,
71 High Holborn,
London
WC1V 6NA.

28th August, 2007.

Dear Reetan,

Medtronic response to Appraisal Consultation Document (ACD): Coronary Artery Stents for the Treatment of Ischaemic Heart Disease (Update to Guidance No. 71).

We have read with interest the ACD and evaluation report (ER) received on the 7th August 2007 and outline our comments below. Medtronic fully disagrees with the draft guidance set out in the ACD. We do not believe that we will be alone in this opinion. After reviewing the comments submitted to the institute by other consultees in the ER it is clear that consultees have been consistent in their opinions that the process has been flawed and that the Liverpool group have not adhered to the core principles of evidence based medicine in their preparation of the assessment report (AR).

As you are aware, Medtronic has repeatedly expressed significant concerns over the way this appraisal has been conducted, data selection and interpretation and the resulting analysis of the cost-effectiveness of DES by the Liverpool group. We do not believe it is worth fully reiterating our major concerns regarding data selection and interpretation in this response, as in the main, despite repeated 'consultation', they have been ignored in the past. We request that this response is considered alongside all previous Medtronic responses to the AR and the numerous addenda and the attached BCIA response with outlines outstanding data concerns with which Medtronic is in full agreement.

Medtronic will address our concerns around two key areas:

1. Appraisal process issues
2. Going forward, potential options

Appraisal process issues

Please find below the timelines for this appraisal currently posted on the institute's website.

Consultation on draft scope by stakeholders:	**January 2005**
Information meeting for consultees:	**31 March 2005**
Closing date for invited submissions:	**5 July 2005**
Final scope posted on website:	**February 2005**
1st appraisal committee meeting:	**01 February 2006**
2nd appraisal committee meeting:	**03 October 2006**
3rd appraisal committee meeting:	**04 July 2007**
4th appraisal committee meeting:	**04 September 2007**
Expected guidance issue:	**January 2008**

The process started in January 2005, and should, in line with published NICE timelines taken approximately one year to complete. Due to delays in the process, including the temporary halting of the appraisal due FDA and MHRA announcements, but more significantly the need for numerous addenda from the Liverpool group due to their insistence on inappropriately prioritizing inappropriate data in their analyses, the process, if adhering to current timelines will have taken three years.

Medtronic strongly believes that the Liverpool related delays could have been avoided should proper consideration of Medtronic's letter of 7th June 2005 written to Professor Sir Michael Rawlins to express concern regarding the conflict of interest of the Liverpool assessment group in this appraisal had been given due consideration. We continue to believe that members of the Liverpool group cannot be impartial since 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. The subsequent delays to the process have meant that the current AR does not include all relevant data. In our previous response Medtronic outlined the high quantity of new data available for this appraisal, it therefore seems perverse and unfair that the new evidence is not incorporated into the AR so that the appraisal committee can base their judgement on all relevant evidence available. If this is not done, it is inevitable that any guidance issued will be out of line with the current evidence base and as a result be out of date before it even starts being implemented by the NHS in England and Wales.

Going forward, potential options

Medtronic believe there to be three potential options moving forward. The most appropriate, due to the delays in process and the need for all current relevant evidence to be included, would be for a complete re-analysis of the clinical and cost-effectiveness sections of the AR. Whilst we fully understand this would be time consuming, we believe it is necessary to avoid inappropriate guidance being issued. In the interim, the current guidance would stand so there would be no negative effects to patients whilst the work was undertaken.

There are two potential ways in which this re-analysis could be conducted. The most preferable option, given the inherent bias of the Liverpool group from the start of this appraisal would be for the process to be started again (including re-submission by consultees) with a new assessment group being commissioned to write the AR. As you are aware, in the Code of Practice for Declaring and Dealing with Conflicts of Interest Issue published in April 2007 section 3.5 states:

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

Under this new code of practice it would be necessary to commission an alternative assessment group as should this code have been in existence at the beginning of the appraisal the Liverpool group could not have been selected as the assessment group for this appraisal as their publication record can clearly be interpreted "as prejudicial to an objective interpretation of the evidence". We believe this would be the fairest option under the circumstances.

As an alternative, as previously suggested to the institute, the Decision Support Unit (DSU) could be engaged to objectively review the work of the Liverpool group. This would go half way to addressing Medtronic's concerns with the process and fairness issues with the appraisal, however, new data would still need to be reviewed and new consultee submissions required which may make the engagement of a new assessment group the most relevant option.

It is unfortunate that the third, and least preferred option, should the provisional guidance remain unchanged, would be for Medtronic to appeal the institute's decision. As you are aware, there are strict grounds set out by NICE which allow consultees to request an appeal:

- The Institute has failed to act fairly and in accordance with its published procedures as set out in the Institute's *Guide to the Technology Appraisal Process*.
- The Institute has prepared a FAD that is perverse in the light of the evidence submitted.
- The Institute has exceeded its powers.

We believe that we have clear grounds under all three categories.

In summary, we have significant outstanding concerns regarding the actions of the Liverpool group in this appraisal, the content of the AR and addenda and the relevance of the ACD guidance. These concerns were raised early in the process and have been consistently relayed to the Institute. Since our manufacturers submission there has been a significant increase in the availability of both clinical and safety data on Endeavor which have been provided by Medtronic during the consultation process, together with simulations of our cost-effectiveness model.

If you have any queries, please feel free to contact Medtronic.

Best regards,

[redacted]
Medtronic Ltd.

[redacted]
Medtronic Ltd.

Reetan Patel,
Technology Appraisal Project Manager,
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9th May, 2007.

Dear Reetan,

Medtronic response to Assessment Report Addenda 3'' and 4': Coronary Artery Stents for the Treatment of Ischaemic Heart Disease (Update to Guidance No. 71).

Thank you for the opportunity to comment on the addendas to the Assessment report. Whilst we appreciate that some minor amendments have been made to the economic model following requests/recommendations made by the Appraisal Committee and the cross industry working group since the appraisal committee meeting and industry response, we believe there to be some significant outstanding issues.

We would like to address our concerns around three key areas:

1. Responsiveness of the LRiG group to requests for reanalyses/data selection
2. New data available to the group since the original submission deadline (July 2005)
3. The impact of the new data on the cost-effectiveness of Drug Eluting Stents (DES)

1. Responsiveness of the LRiG group to requests for reanalyses/data selection

Appendix 1 tabulates the NICE project specification table provided to the LRiG group regarding further work to be undertaken on the original assessment report economic evaluation. The table has been annotated with comments from Medtronic re actions taken by LRiG to address the appraisal committee's concerns.

For example, it is perverse, that despite direct requests for LRiG to use data to assess risk factors for repeat revascularisation from alternative sources, LRiG have failed to do so and have continued to rely on single centre CTC audit data. Similarly, whilst Medtronic appreciate the incorporation of diabetes in the model as an independent risk factor, continued reliance on the CTC data to derive diabetes risk factors is unacceptable, as it is not representative of repeat revascularisation rates and underpowered to detect a difference in revascularisation rates between diabetics and non-diabetics. Furthermore, Table A6.2 *"Summary of risk model factors in reviewed papers"* does not present the results of a further 7 risk models, 5 of which identify diabetes as an independent risk factor for repeat revascularisation. These are but two examples (please refer to Appendix 1 for full listing) where it appears the wishes of both the appraisal committee and industry have been blatantly disregarded with no rationale given for LRiGs decisions.

We strongly believe that from the outset, the LRiG have been unable to make rational decisions due to a conflict of interest. Medtronic would like to refer to their letter of 7th June 2005 written 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. We did not believe, and continue not to believe that members of the Liverpool group can be impartial under

these circumstances. The LRiGs continued insistence that their approach is correct despite it conflicting with the clinical and economic findings of other published literature on DES calls into question the fairness of this appraisal.

In the Code of Practice for Declaring and Dealing with Conflicts of Interest Issue published in April 2007 section 3.5 states:

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

It is clear that the Institute, rightly understand the need for such a code and that should this code have been in existence at the beginning of this appraisal LRiG could not have been selected as the assessment group for this appraisal as their publication record can clearly be interpreted "as prejudicial to an objective interpretation of the evidence". We ask, that in the interests of fairness, this point is raised at the next appraisal committee meeting as a matter of priority in addition to a discussion on the potential role of the DSU in this appraisal.

2. New data available to the group since the original submission deadline (July 2005)

As you are aware, due to significant delays in this guidance review, almost two years have passed since industry have been able to submit any new available data to the Institute for inclusion in the appraisal. Further to letter received by the Institute on 12 March 2007 where we were incorrectly informed that Medtronic would have the opportunity to submit additional data to the Institute, Medtronic prepared a brief summary of new data available which we believe should be drawn to the attention of the appraisal committee (please refer to appendix 2). Whilst we realise that this will not be formally included into the assessment report we would like some key messages to be conveyed to the committee:

The Endeavor clinical program continues to generate strong cumulative evidence regarding Endeavor's overall performance, with consistent and predictable patient outcomes sustained over time. ***Indeed, the growing volume of positive data and number of patients with long-term follow-up continues to demonstrate the deliverability, the clinical efficacy and the strong safety profile of the Endeavor drug-eluting stent.***

The two-year results from the Endeavor III (EIII) trial confirms the positive clinical profile of the Endeavor drug-eluting coronary stent and bring to nearly 1,300 the number of Endeavor patients who have at least two years of follow-up. In EIII, at two years, the rate of Major Adverse Cardiac Events - a composite safety measure of death, repeat procedures and myocardial infarction (MI) – is 9.3% for Endeavor and 11.6% for the Cypher stent (p = 0.47). There is no statistically significant difference in the need for repeat procedures, or Target Lesion Revascularization (7.0% and 4.5% for Endeavor and Cypher, respectively, p = 0.50), or all-cause mortality (1.6% for Endeavor and 4.5% for Cypher, p = 0.14**). *However, fewer patients experienced heart attacks (MI) when treated with the Endeavor stent (0.6% vs. 3.6% for Cypher, p = 0.04) and the combined rate of heart attack and death also is statistically significantly lower among patients randomized to the Endeavor stent (2.2% vs. 7.1% for Cypher, p = 0.013).***

The reported pooled safety and efficacy data at one year on more than 1,300 patients from the Endeavor I, II, and III trials (including Endeavor II Continued Access) also confirms ***Endeavor's excellent safety record, with no observations of late stent thrombosis (more than 30 days***

after implant), and an overall thrombosis rate of just 0.3%. It demonstrates no significant differences in TLR or late loss across high risk subgroup parameters, such as vessel diameter size, lesion length and patient diabetic status.

The 3-year data from the 100-patient first-in-man Endeavor I (EI) clinical study, and the 2-year results from the 1,200-patient, double-blind randomized Endeavor II (EII) pivotal trial, with a patient follow-up for both trials of 97%, show low rates of restenosis and an excellent safety profile.
At 36 months, the combined rate for myocardial infarction, death and TLR in the EI study is 6%, while the 24-month MACE rate in EII is 10%. In EII, 93.5 percent of the Endeavor patients remain free of repeat procedures after two years, with a TLR rate of only 6.5 percent. In addition, in the ***EII study, there is no difference in mortality between the Endeavor (2.1%) arm and the Medtronic Driver (2.2%) bare metal stent arm, and the study also shows a 47 percent reduction in MACE between Endeavor arm (10.0%) and the Driver arm (18.7%).***

As a final point, Endeavor is safe by definition, when using either the definition of stent thrombosis used by the clinical trial HRCI CEC , or re-adjudicated expanded ARC stent thrombosis definition, or even simply the composite rate of death and Q-wave MI.
Concerning the ARC reclassification and in terms of cumulative incidence out to three years, proportionally more events were added in the bare metal stent groups than in the Endeavor DES groups; the difference in event rates was significant (1.0% vs 3.3%; P = 0.01). The overall increase is driven mostly by increased late and very late 'possible' events, with definite or probable events similar to prior reports using protocol definitions and trending lower for the DES arm.

The update on the safety data is especially pertinent to the Endeavor stent in this appraisal. In your communication of 11th April 2007, you stated that with respect to the economic modelling "Following the recent concerns over the safety of DES these sensitivity analyses have been extended to examine how the difference in the duration of clopidogrel use between BMS and DES may affect the cost effectiveness (see attached, Addendum 4'). This reflects recommendations made by the American Heart Association and the British Cardiovascular Intervention Society, that the duration of use of anti-platelet therapy (aspirin and clopidogrel) should be extended in patients who have received a DES to at least 12 months, and in particular in those patients whose lesions are thought to be high risk". What the Institute failed to mention was that the FDA and BCIS recommendations were made on the basis of three studies (Camenzind, Nordmann and Wenaweser) none of which include Endeavor related safety data.

In Medtronic's current IFU, it states that "In clinical trials of the ENDEAVOR stent, clopidogrel or ticlopidine was administered pre-procedure and for a period of at least 12 weeks post-procedure. Aspirin was administered concomitantly with clopidogrel or ticlopidine and then continued indefinitely to reduce the risk of thrombosis".
In view of this shorter duration of clopidogrel usage, the lack of data to show safety concerns associated with the Endeavor DES and the FDA statement that "The optimal duration of antiplatelet therapy, specifically clopidogrel, is unknown and DES thrombosis may still occur despite continued therapy", may we strongly suggest that sensitivity analysis is conducted at a range of clopidogrel administration doses.

3. The impact of the new data on the cost-effectiveness of Drug Eluting Stents (DES)

In view of the new information available on the long-term efficacy and safety of Endeavor stent, we have re-analysed the cost-effectiveness model comparing the Endeavor stent to the Driver stent which was also included in the original submission. The model used the same inputs and assumptions as LRiG's model with the exception of using TVRs instead of total revascularisation rates and a longer time-horizon. Instead of extrapolating the observed 9-month outcomes from the Endeavor II trial to one year and then assuming that no difference exists between Endeavor

and Driver between years 2 and 5, the up-dated model now relies on observed trial outcomes at 24 months pooled from the Endeavor II and Endeavor III trials. All other model inputs and assumptions remained the same. The trial evidence of sustained effectiveness had a favourable impact on the cost-effectiveness of the Endeavor stent versus the Driver stent with an incremental cost-effectiveness ratio below £10,000/QALY gained at 5 years. The results were also confirmed in a probabilistic analysis which showed Endeavor to have a 76% and 86% probability of being cost-effective compared to Driver, using a £20,000/QALY and a £30,000/QALY threshold, respectively.

In summary, we have significant outstanding concerns regarding the actions of the LRiG in this appraisal. These concerns were raised early in the process and have been consistently relayed to the Institute. Since our manufacturers submission there has been a significant increase in the availability of both clinical and safety data on Endeavor which translates into a strong cost-effectiveness argument for the use of this product in the NHS. We submit this response alongside the cross-industry response from BCIA with which, in the main, we are in concurrence. With respect to section 4.1 of the BCIA response, we kindly request that you also refer to section two of the Medtronic response regarding the duration of clopidogrel administration.

If you have any queries, please fell free to contact me.

Best regards,

[redacted]

Medtronic Ltd.