Joint British Cardiovascular Society (BCS) and British Cardiovascular Interventional Society (BCIS) response to

"Ischaemic heart disease- coronary artery stents (review) Appraisal Consultation Document"

Dear Dr Longson

This document constitutes the British Cardiovascular Society and British Cardiovascular Intervention Society official response to the above "Appraisal Consultation Document".

Members and executives of these societies remain deeply concerned with the conclusions of the draft guidance and resolutely determined to highlight the inadequacies of the Liverpool Assessment Group and the means by which the conclusions were reached. We truly fear that should the Guidance be implemented this will be a major and fundamentally important retrograde step for British Cardiology.

We will address the document under the headings suggested.

(i) <u>Do you consider that all the relevant evidence has been taken into account?</u>

We had always been led to believe that appraisals developed by The National Institute for Clinical Excellence were fundamentally based on robust evidence and that their core analysis was driven appropriately by data from worldwide randomised trial literature. This has not been the case within this appraisal. We continue to be confused by the emphasis that has been placed on a single unsubstantiated audit and a single trial in the literature (the Basket Trial).

The Liverpool CTC database was designed to assess the in-patient complications and local clinical outcomes of coronary angioplasty. Since it cannot be regarded as being robust in terms of known and confirmed outcomes, this local audit has in the setting of this appraisal, which depends on robust knowledge of absolute outcome data, been used inappropriately. We have previously explained to the Committee (on a number of occasions) that there was no systematic follow up of patients, that some patients developed symptoms but did not undergo a repeat revascularisation within a year (because of waiting list issues) and that patients who received a repeat revascularisation at another hospital did not appear on the database. Such factors, together with a systematic bias against high risk patients (demonstrated by the low diabetes rate in the cohort), result in an unrealistically low repeat revascularisation rate of 7.43%. Dr Rod Stables and other cardiologists at CTC confirm the inadequacy of the Liverpool database for a NICE type of appraisal. The committee also appears to acknowledge this because they eventually decide on a rate for repeat revascularisation in a general population in the final appraisal document of 11%. The risk factors for repeat revascularisation that "fell out" of the Liverpool Assessment Group analysis using the CTC database are unquestionably unique in the world literature. Multiple properly performed trials and registries have repeatedly shown small vessels, long lesions and diabetics to be the populations at high risk of needing a repeat procedure. This either means the Liverpool patients are unique or that there is a systematic bias in patient selection and treatment methods. Once more the committee appear to acknowledge this by dismissing the idea that there may be a difference between elective and non-elective patients, something that only the Liverpool Assessment Group analysis of the CTC database has found. The situation becomes confusing and compounded since subsequently data from the Liverpool

database is used to calculate the relative risk of repeat revascularisation in patients with small vessels, long lesions and diabetes. Once more the committee appear to have agreed that these are high risk patients (merely by asking the Liverpool Assessment Group to carry out a subsequent analysis on the world recognised high risk groups). What should have happened then of course was for the committee to ask the Liverpool Assessment Group to undertake this high risk group analysis using the independently adjudicated, peer-reviewed and published, randomised controlled trial data. Even the much touted Basket trial agrees that these factors do increase subsequent revascularisation and that these are the very patients who benefit from the use of drug eluting stents (DES). To then use the Liverpool data for repeat revascularisation in these high risk groups rather than the world literature appears utterly perverse, inappropriate and illogical as we already know that due to the systematic bias of the registry these factors had not appeared to increase the risk of revascularisation. Therefore the data and the numbers that are generated must be suspect.

At the beginning of this appraisal the British Cardiovascular Intervention Society contacted NICE to indicate that we felt that the Liverpool Assessment Group had a fundamental conflict of interest and were not the appropriate group to carry out the review. Given that this group had already published a negative manuscript on the cost effectiveness of DES using the flawed CTC data, it is difficult to see how they could ever carry out an independent review. We presume that under the new conflict of interest rules of NICE Liverpool would currently be excluded from any such similar appraisal.

If the committee continue to use this data for the basis of their evaluation, rather than the randomised literature, we believe the appraisal remains deeply flawed and thus, in this context, is worthless. In addition we believe this use of inadequate data and overall poor methodology will do great harm to the credibility of the NICE process.

(ii) **Do you consider that the summaries of the clinical and cost effectiveness are reasonable interpretations of the evidence and that the preliminary views on the resource impact and implications for the NHS are appropriate?**

It has been acknowledged in the Appraisal that DES are indeed clinically effective in reducing repeat revascularisation following percutaneous coronary intervention and that this difference reaches levels of high statistical significance.

The cost effectiveness model is critically dependent on 4 key variables. We believe the the numbers used for these variables in the Liverpool Assessment Group model are incorrect due to use of the flawed baseline CTC data. The committee have changed these values during the course of the appraisal but the final values remain illogically derived and appear to represent compromise values rather than being based on evidential science. We do not believe this is the methodology under which such a National Appraisal by NICE should take place.

(a) *The absolute risk of repeat revascularisation with bare metal stents*

The value used by the committee for target lesion revascularisation is 11%. We are unclear how this was derived, but paragraph 4.3.6 of the Appraisal Consultation Document suggests that it is a “compromise figure”; in any event it has not been derived from published data or recognised scientific methodology. It would appear that the Committee appropriately disbelieve the Liverpool Assessment figures but

cannot quite come to accept the figures from the randomised controlled trials and from the substantial and peer reviewed published registry data.

We initially shared with the committee the data from such randomised trials and real world registries, both with and without angiographic follow up, indicating that the baseline bare metal stent repeat revascularisation rate is > 12%. We understand that some members of the committee felt that high repeat revascularisation rates were driven by trial protocol, particularly routine follow-up angiography. We have however provided to the committee similar figures for repeat revascularisation in the randomised trials that did not mandate angiographic follow up.

The Committee subsequently referred us to the Scottish Revascularisation Registry; this reports a repeat intervention rate, after implantation of a bare metal stent and without mandated angiography, of 13% and, in contrast to the Liverpool CTC data, has been both peer reviewed and published. We should emphasize that the Committee were drawn towards The Scottish Revascularisation Registry data as it is not based on mandated angiograms and reflects UK clinical practice in the ”real world”; it is therefore the most appropriate source for the real world figure when setting the baseline rate for repeat revascularisation without DES.

(b) *The relative risk of certain high risk groups*

The worldwide literature repeatedly reports that patients with long lesions, small vessels and diabetes have a particular high risk of repeat intervention (relative excess risk of 1.75 for small vessels, 1.35 for long lesions and 1.52 for diabetes). We therefore believe that the correct figures for the risk of repeat revascularisation with a bare metal stent to be used in any model must be 22.8% for small vessels (from 1.75 x 13%); 19.8% for diabetes and 17.6% for long lesions. We presented this to the Committee as tables with references, and broken down into those studies that were angiographically driven and those where the repeat revascularisations were clinically driven. The Assessment group were encouraged to do something similar but perversely elected to use figures from the Liverpool database that, in stark contrast to the world literature, did not indicate any increased risk for these recognised as high risk groups. We have consistently argued that the Liverpool data are poor for this type of analysis and systematically biased against the high risk groups. These values are so vital to the subsequent cost effective analysis that we would urge NICE to revisit them using the worldwide literature. High risk patients (small vessels, long lesions, diabetics) have a 30% to 75% extra chance of requiring a repeat procedure as a result of recurrent symptoms. This was recognised in earlier guidance from NICE and justifies the use of drug eluting stents in these selected patients.

(c) *The benefit of a drug eluting stent over a bare metal stent - what is the real reduction in need for subsequent revascularisation using DES?*

After consulting the extensive published literature, we argued that DES reduced the chances of needing a repeat revascularisation by between 61-70%. Again, we presented the evidence for this in the form of a table with references. The committee eventually used a value of 55%; we can see no logic or explanation for the use of this figure other than compromise between the Liverpool Assessment Group nonsensically low original 35% reduction in need for repeat revascularisation and the published figures of 60%-70%. Use of unjustified compromise or averaging of values should clearly not be the basis for such an important assessment – the correct and published data should be used. The Assessment group argued that the effect of drug eluting stents was over-estimated by the angiographic follow up used in the randomised trials. The data we presented were based on trials and registries with

and without angiographic follow-up so we fail to understand the Committee's position. Indeed, the Appraisal text contains figures that testify to the absolute benefit of DES - a one year reported TLR for BMS of ~20% and for DES ~5% - this equates to a 75% reduction, yet the figure of 55% is used with no explanation and for no apparent reason.

(d) *The cost differential between drug eluting stents and bare metal stents.*

We feel this is a crucial, but to date harder to clarify, part of the entire appraisal. Using our cost/efficacy model, which we based on that used by the Liverpool Assessment Group (and which we have confirmed as being "acceptable" by modelling in their figures and deriving their, albeit inappropriate, results) and populating it with the figures we have justified above we were able to show that a cost effectiveness of £30,000 per QALY could be met in small vessels, long lesions and diabetes with a price "delta" of £491, £363 and £354, respectively. We believe that the current price premium of drug eluting stents within the NHS is below all three figures. The prices quoted by the Liverpool Assessment group and the committee are 2 years out of date and grossly inflated. The price for a Taxus stent (£815) and a Cypher stent (£937) used in the economic model therefore bear no resemblance to the true costs of these devices within the NHS price structure which are around £550 and £600. The suggestion used throughout the appraisal that Scotland has achieved a lower cost of drug eluting stents compared to the rest of the United Kingdom is simply not true. Furthermore, in February 2006 NICE reported that the Liverpool price differential of £500 was too high and that is likely to be nearer £300. This is quoted in a publicly available document. We believe the committee should seek up-to-date prices for DES within the NHS. BCIS have recently carried out just such a survey. The results are attached in Appendix 1 and show a "true" cost of DES in the NHS to be £550-600. In addition, 3 Scottish centres appear in the data and they are not the lowest 3 prices.

We strongly believe that running the model with the true base rate for bare metal stent, true published benefit for DES and the true price difference will prove the cost efficacy of these devices.

(iii) **Do you consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS**?

We believe this cannot be the case and that using inappropriate data will lead to unsound recommendations. We believe the data used by the Liverpool Assessment group and the process of deriving the Committees conclusions should be subjected to **independent review.**

In addition we believe that a **threshold analysis** should be undertaken, using the correct clinical data variables as outlined above, which will indicate the price premium at which DES are cost effective within the current pricing structure of the NHS. We believe that this derived price premium would in the circumstances of using correct data actually be in line with the real current cost of DES in the UK. Only by doing this could any Appraisal be a "suitable basis for the preparation of guidance to the NHS".

A paradoxical effect of this unsound guidance will be to drive up the overall cost of coronary revascularisation to the NHS. If this draft appraisal is upheld clinicians will not return to the use of bare metal stents. They will use data from the ARTS1 trial and refer large quantities of patients back to cardiac surgery. This will result in

increased morbidity to our patients, increased waiting times, failure to achieve Government driven targets, and a clear increased cost to the NHS. Our calculations suggest that >10,000 patients will be referred back to surgery at a cost of £60 million.

(iv) Are there any equality related issues that may need special consideration?

We have two areas of concern when considering equality issues. The first is equality of NHS patients compared to the rest of the world. If this draft guidance is applied to NHS practice then many patients in the UK may well undergo coronary artery bypass grafting or repeat angioplasty compared to similar patients in the rest of Europe and the USA. This will result in potential unnecessary harm to UK patients. Indeed, if DES cannot be accessed in the NHS then patients will have to resort to seeking treatment in the private sector or indeed may travel abroad in order to have access to DES. This will undoubtedly result in a 2 tier system of healthcare between the NHS and private sector with regard to coronary revascularisation. DES should be available to all in whom they can be shown to be cost effective which is irrefutably the case in those patients with small vessels and or long lesions to be stented or who are diabetic. A combination of these risk factors which is often found in real world patients leads to an published 45% chance of needing a repeat procedure – it would be unacceptable for patients in whom cost efficacy can be shown to be denied treatment and is against the very ethos of what NICE is meant to be trying to achieve.

The other equality issue will be for those patients who are currently turned down for cardiac surgery. If there is no funding for DES these patients are likely to receive no treatment at all. Given the complex nature of many of these patients clinicians will be reluctant to use bare metal stents because of the high incidence of recurrence.

Failure to reverse the current draft guidance will result in inappropriate harm to patients because of the excess need for repeat revascularisation procedures and unnecessary referrals for coronary artery bypass grafting. In addition the UK would be practising dramatically different medicine to the rest of the world and much of the improvements in UK revascularisation achieved in the last 10 years would be reversed.

We truly believe that DES are not cost effective in ALL patients but equally they are absolutely cost effective in the high risk groups highlighted. The National Institute for Clinical Excellence has during this appraisal process been guided towards the correct values to derive an analysis of potential cost efficacy by BCIS. That they have chosen to ignore the independent published data presented by the medical experts, all of whom are recognised as renowned clinical scientists, and instead use, initially, poor data from Liverpool group and then unjustified apparent compromise figures, is truly disconcerting. On behalf of patients we request that NICE recognise the validity of our presented arguments and that they uphold their previous guidance which directed the use of DES in the recognised high risk groups of small vessels and long lesions with the added now recognised high risk diabetic patients population. Not to do so will undermine credibility in the whole process and place UK cardiology back 5 years. We will be totally isolated from world wide contemporary practice until the next review. This will be disastrous for patients and physicians and, we believe, for NICE.

	DES Price
Hospital A	£540-600
Hospital B	£650
Hospital C	£550-700
Hospital D	£625-650
Hospital E	£575-700
Hospital F	£550-650
Hospital G	£500-670
Hospital H	£595
Hospital I	£550-650
Hospital J	£550-650
Hospital K	£590-600
Hospital L	£590
Hospital M	£575-600
Hospital N	£550
Hospital O	£580
Hospital P	£600
Hospital Q	£500-730
Hospital R	£540-600
Hospital S	£550-700
Hospital T	£590
Hospital U	£700
Hospital V	£540-600
Hospital W	£550-650
Hospital X	£450-500
Hospital Y	£550-600
Hospital Z	£600-650