Drug-eluting stents:

a systematic review & economic evaluation

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Addendum

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Additional evidence and analyses consequent on ACD consultation responses

1. Introduction

A number of responses have been received by NICE from consultees following the release of the draft guidance contained in the ACD issued in August 2007 relating to the use of drug-eluting stents. Several of these responses contained detailed comments on the parameter values used in the Assessment Group's model, with proposed alternatives. The majority of these comments were derived from a common source (the document entitled "BCIS Comments on the Economic Model"). In order to consider the implications of these comments and suggestions, LRiG was asked to generate additional sets of cost-effectiveness results addressing the issues raised in the BCIS paper incorporating appropriate alternative parameter values; two sets of tables are provided in this Addendum, as requested by the Appraisal Committee chair.

2. Analysis 1 - Limited Application of BCIS Proposals

2.1 Assumptions and Values

2.1.1 Updating resource costs

The BCIS consultation response states: "The model ..... must be re-run using the most contemporary 2005-06 reference costs." They provide the following table of unit costs which they believe to be appropriate:

Cost Item	**Current Model Input (2003-04 Costs)**	**2005-06 Reference Cost**
Cardiology out-patient visit	£134	£148 (code 320F)
Cardiac surgery out-patient visit	£208	£274 (code 172F)
Angiography	£724	£838 (day case E14)
Unstented PCI	£1453.40	£1937.40
CABG	£7066	£8172
Cardiology out-patient f/up visit	£94	£104 (code 320F)
Cardiac surgery out-patient f/up visit	£156	£182 (code 172F)

These values have been adopted for this analysis with the following provisos:

- the Cardiology out-patient cost for initial investigation given in the BCIS table relates only to the first attendance in a sequence. Since the LRiG model includes 5% of patients who require a second cardiology visit before proceeding to intervention, the correct cost should be a weighted average of the first attendance cost (£147.78) and the repeat attendance cost (£103.42) giving an overall average of £145.67.

- it is not clear how BCIS have obtained their estimated average cost for an unstented PCI of £1,937.40. To be consistent with other variables in the model, this should be based on subtracting the estimated average cost of stents used from the average cost of a PCI. This involves multiplying the average number of stents per patient treated by the average cost per stent, which in turn depends on the unit costs of BMS and DES, and the relative proportions of the types of stent deployed. The model base case involves a BMS cost of £291.95 and a DES price premium of £600. It is also assumed that the overall average number of stents per patient is about 1.6, and that currently about 60% of stents used are DES (BCIS Audit 2006 (1)). Since the Reference Costs of PCI differ between elective and non-elective cases, it is also necessary to estimate how many patients requiring a repeat intervention follow the non-elective (emergency or urgent) route. No secure source is available for this factor, but we can reasonably expect that most of the 11.5% of patients who complete their repeat treatment within the first 6 weeks will not have followed the elective route, and a proportion of the remainder (taken as at least 5%) will also be non-elective cases - this gives a conservative breakdown of 84.0% elective / 16.0% non-elective. It proved impossible to identify a consistent combination of values which would replicate the BCIS estimate. Our calculations suggest that a higher figure of £2099.19 is more appropriate and this has been employed in both analyses presented here.

2.1.2 Duration of recurrent anginal symptoms

In the BCIS paper, the authors argue that the current model estimates for the mean time from recurrence of severe anginal symptoms to retreatment are understated in the light of recent NHS statistics. They rely on a simple approach to estimation employed by Hawkins, Sculpher and Rothman (2), which adds together separate estimates for

the time from GP referral to first out-patient cardiology visit, the time spent waiting for angiography and the time spent waiting for the second revascularisation procedure, quoting figures in their Table 4 showing a total wait for PCI of 25.1 weeks and for CABG of 26.4 weeks.

There are several reasons to consider that the BCIS figures are unreliable and inappropriate for use to represent current UK experience for these patients:

1) **The authors of the BCIS paper have miscalculated the mean waiting time to first cardiology out-patient appointment.** The distributional figures shown in the BCIS table bear little relation to NHS source data. Using the NHS Provider-based Outpatient Statistics, Quarter 1 2007/08 we estimate the mean waiting time to be 25.6 days (3.7 weeks) rather than the 42 days (6 weeks) given by BCIS - this reduces the overall total mean wait from 26 weeks to 23 weeks.

2) **Estimates in the region of 26 weeks are not credible in the light of published evidence of the pattern of occurrence of repeat revascularisations.** Analyses of time to event for second intervention in a recent analysis of the Ontario database (Figures 9 and 10 of the McMaster report (3)) indicate that events are evenly spread across the first 12 months of follow-up showing a roughly constant hazard over time (very similar to patterns observed in the Liverpool CTC audit data). This implies that the total available follow-up time free of intervention for patients undergoing a second intervention cannot exceed 26 weeks, at which value *every* such patient is obliged to have suffered severe anginal symptoms from the day of the index procedure until the second PCI/CABG. This excludes the possibility of any benefit from the index procedures, and implies that on discharge from the index procedure all such patients go direct to their GP and demand to be re-referred to the hospital. Clearly this does not happen. In fact, although the average total time to event in the Canadian database for patients revascularized in the first 12 months is about 22.6 weeks (cf. 22.3 weeks in CTC audit), the recorded time spent waiting for care is only about 14 days (non post-MI patients in Table 48) to which a nominal 30 days are added in their economic analysis to reflect symptoms leading up to the decision to re-admit the patient. Clearly UK access times will not be so brief, but it is very likely that the total time with symptoms will be substantially less than the 26 weeks BCIS estimate, and somewhere in the range 6.3 - 22.6 weeks seen in the Canadian data.

3) **The BCIS estimates wrongly assume that all patients requiring a repeat intervention will be treated as elective cases.** Discussions with cardiologists from several UK centres indicate that patients presenting within the first few weeks following their index procedure will normally be seen and treated as urgent cases, and are unlikely to be added to the elective waiting list. In addition an unknown proportion of patients with recurrent symptoms following this initial period will present as non-elective/emergency chest pain admissions requiring early retreatment during the same hospital stay. Assuming as above that patients representing within 6 weeks of their first PCI are treated non-electively, as are 5% of those presenting later than 6 weeks, we estimate that the overall average waiting time for treatment would be about 15% lower than the BCIS figures.

4) **The BCIS estimates also assume that returning PCI patients will wait on average the same period of time as other elective patients for treatment.** Patients undergoing PCI for restenosis represent only a very small proportion of the overall caseload (about 4.5% according to the BCIS Audit 2006 (2)). There are no national statistics on waiting times disaggregated for any subgroups, but if any patients are accorded any degree of relative priority it is very likely that these would include patients suffering from recurrent severe symptoms (from all those awaiting an outpatient appointment or those requiring angiography), and those indicated for retreatment of restenotic lesions (by PCI or CABG). LRiG have recently sought advice on the current management of such cases from interventional cardiologists at several UK specialist centres which confirms this view. Responses received include the following:

> Centre A: "I would see patients in my clinic (referred by either the GP or secondary care cardiologist). Although patients do have to wait a while, I have specific slots in my clinic for these types of patients. If I thought they did have cardiac pain I would book them onto the cardiac cath list. I try to get a patient's consent before this appointment so that if there is a problem it can be dealt with then and there i.e. there would be no referral for further treatment as it would all be performed at the same time. If I am unsure that the patient has cardiac pain, then I refer them for a DS Echo first and then follow the same procedure."
>
> Centre B: "I would see patients in clinic and then fast track them onto a list which would allow the patient to get an angiogram and a PCI at the same time. .... Yes, such patients do tend to be seen more quickly. Patients with history wouldn't have to start from scratch again. .... This is more 'custom and practice' rather than a formal unit protocol."

5) **Government policy imposes a maximum total waiting time from GP referral to treatment for elective interventions of 18 weeks with effect from 2008.** Clearly the BCIS estimated total wait time is inconsistent with this requirement, which implies that the average total wait will be less than 18 weeks taking account of statistical variation below the upper limit, as well as those urgent/emergency cases treated non-electively.

Remedying the BCIS arithmetic error and taking account of those patients treated non-electively, we arrive at a corrected estimate for the mean overall waiting time of 20.5 weeks for second PCI and 20.9 weeks for CABG. This should be compared to the mean delays assumed in the current LRiG model - 20 weeks for second PCI and 13 weeks for CABG. It is likely that both these sets of estimates may be unjustifiably generous, in view of the need to moderate unspecific average waiting times when estimating the necessarily shorter time during which patients suffer with severe symptoms, and also the imminent national maximum wait policy. Nonetheless, for the purposes of illustrating the effect of implementing the BCIS suggestions, the corrected BCIS times (20.5 & 20.9 weeks) are used to generate the following results.

2.1.3 Estimation of stent usage per patient

The BCIS paper presents an alternative set of values (as Table 5) for the average stent usage for each of the eight conventional subgroups, based on calculating a weighted average of the elective and non-elective figures in the proportions 67.5 : 32.5. Unfortunately this approach in inaccurate as it does not allow for the differing casemix patterns of elective and non-elective patients. The correct approach is to weight the stent use separately in each subgroup in proportion to the number of actual cases.

On examination it transpires that the means shown in Table A of the previous Addendum were not correctly calculated and we are grateful to the BCIS authors for pointing this out. However, these errors in no way affect the parameter values in the model, which calculates incremental costs and outcomes separately for elective and non-elective patients before final combination to produce aggregated results.

Therefore, there are no amendments required in the model or to the cost-effectiveness results - only to the column of figures in Table A which were provided for information only. LRiG apologies for this mistake; the accurate figures are as follows:

Conventional risk factors			
Long lesion	Small vessel	Diabetes	Mean stents used
No	No	No	1.51
Yes	No	No	1.57
No	No	Yes	1.55
No	Yes	No	2.23
Yes	No	Yes	1.66
Yes	Yes	No	2.52
No	Yes	Yes	2.57
Yes	Yes	Yes	2.50
Overall			1.571

For comparison, it should be noted that the mean number of stents per case reported in the BCIS Audit 2006 (1) is 1.63.

2.1.4 Existing clopidogrel use

The BCIS have revised their previous estimate (44%) of the proportion of presenting patients who will already be receiving continuous clopidogrel anti-platelet therapy in accord with NICE ACS guidance, and therefore will not incur additional medication costs - the new estimate is given as 48.5% and this figure is used in all these analyses.

2.2 Results

The results of Analysis 1 are shown in Tables A.1 & A.2, in the same format as used in earlier Addenda using the two requested options for global relative risk reduction due to DES (55% and 65%). Only relatively minor changes are apparent compared to earlier results.

Tables A.1 & A.2: Results of Analysis 1 incorporating updated costs, modified anginal exposure times and clopidogrel use

Combined Elective & Non-Elective Index PCI

1.571 stents per patient on average **55% relative risk reduction at 12 months due to DES**

Conventional risk factors			Absolute risk	Incremental utility	Incremental cost by levels of price premium								Incremental cost per QALY by levels of price premium							
Long lesion	Small vessel	Diabetes			£100	£200	£300	£400	£500	£600	£700	£800	£100	£200	£300	£400	£500	£600	£700	£800
No	No	No	9.7%	0.00422	£65	£211	£358	£504	£651	£798	£944	£1,091	£15,300	£50,100	£84,800	£119,600	£154,300	£189,100	£223,800	£258,600
Yes	No	No	11.7%	0.00494	£22	£173	£325	£477	£629	£781	£932	£1,084	£4,400	£35,100	£65,800	£96,600	£127,300	£158,100	£188,800	£219,600
No	No	Yes	11.6%	0.00492	£22	£171	£321	£471	£620	£770	£920	£1,070	£4,400	£34,800	£65,200	£95,600	£126,000	£156,400	£186,800	£217,200
No	Yes	No	19.0%	0.00770	-£108	£104	£316	£528	£740	£952	£1,165	£1,377	-£14,000	£13,600	£41,100	£68,600	£96,100	£123,600	£151,200	£178,700
Yes	No	Yes	13.9%	0.00579	-£26	£134	£294	£454	£614	£775	£935	£1,095	-£4,400	£23,200	£50,900	£78,500	£106,200	£133,900	£161,500	£189,200
Yes	Yes	No	22.7%	0.00910	-£172	£70	£313	£555	£797	£1,039	£1,282	£1,524	-£18,900	£7,700	£34,400	£61,000	£87,600	£114,200	£140,900	£167,500
No	Yes	Yes	21.4%	0.00862	-£143	£93	£329	£565	£800	£1,036	£1,272	£1,508	-£16,600	£10,800	£38,100	£65,500	£92,900	£120,200	£147,600	£175,000
Yes	Yes	Yes	25.6%	0.01020	-£229	£28	£284	£540	£796	£1,053	£1,309	£1,565	-£22,400	£2,700	£27,800	£53,000	£78,100	£103,200	£128,400	£153,500
Overall			11.0%	0.00468	£40	£192	£344	£496	£649	£801	£953	£1,105	£8,400	£41,000	£73,500	£106,100	£138,600	£171,200	£203,700	£236,300

Patients affected by factor

27.9%	4.9%	13.1%

Combined Elective & Non-Elective Index PCI

1.571 stents per patient on average **65% relative risk reduction at 12 months due to DES**

Conventional risk factors			Absolute risk	Incremental utility	Incremental cost by levels of price premium								Incremental cost per QALY by levels of price premium							
Long lesion	Small vessel	Diabetes			£100	£200	£300	£400	£500	£600	£700	£800	£100	£200	£300	£400	£500	£600	£700	£800
No	No	No	9.7%	0.00489	£19	£164	£310	£456	£601	£747	£893	£1,038	£3,900	£33,700	£63,500	£93,300	£123,100	£152,900	£182,700	£212,500
Yes	No	No	11.7%	0.00574	-£33	£117	£268	£419	£569	£720	£871	£1,021	-£5,800	£20,500	£46,700	£73,000	£99,300	£125,500	£151,800	£178,100
No	No	Yes	11.6%	0.00572	-£33	£116	£264	£413	£561	£710	£858	£1,007	-£5,700	£20,200	£46,200	£72,200	£98,200	£124,100	£150,100	£176,100
No	Yes	No	19.0%	0.00900	-£198	£13	£223	£433	£643	£853	£1,063	£1,273	-£21,900	£1,400	£24,700	£48,100	£71,400	£94,700	£118,100	£141,400
Yes	No	Yes	13.9%	0.00674	-£91	£68	£226	£385	£544	£702	£861	£1,020	-£13,500	£10,100	£33,600	£57,200	£80,700	£104,200	£127,800	£151,300
Yes	Yes	No	22.7%	0.01065	-£279	-£39	£201	£441	£681	£921	£1,161	£1,401	-£26,200	-£3,700	£18,800	£41,400	£63,900	£86,400	£109,000	£131,500
No	Yes	Yes	21.4%	0.01009	-£244	-£10	£224	£457	£691	£925	£1,158	£1,392	-£24,200	-£1,000	£22,200	£45,300	£68,500	£91,700	£114,900	£138,000
Yes	Yes	Yes	25.6%	0.01195	-£350	-£96	£158	£412	£666	£919	£1,173	£1,427	-£29,200	-£8,000	£13,200	£34,400	£55,700	£76,900	£98,100	£119,400
Overall			11.0%	0.00543	-£12	£139	£290	£441	£593	£744	£895	£1,046	-£2,200	£25,600	£53,500	£81,300	£109,200	£137,000	£164,900	£192,700

Patients affected by factor

27.9%	4.9%	13.1%

3. Analysis 2 - Extended Application of BCIS Proposals

3.1 Assumptions and Values

In this analysis some additional BCIS issues are addressed, and an additional set of results presented. Due to the lack of compatible and consistent data, it is not possible in this short addendum to provide results for an exhaustive set of risk-related subgroups.

3.1.1 Baseline risk of revascularisation and presentational casemix

The BCIS authors comment on the balance between elective and non-elective presentations in the current model: "The CTC proportion of 32.35% non-elective is low compared with the national picture in which 48.5% (BCIS audit figures for 2006) present as acute coronary syndromes." This comment betrays a misunderstanding of the basis of derivation of the CTC casemix proportions. This involves excluding STEMI patients for whom PCI represents a primary treatment for AMI, and then considers that elective patients generally present for stable angina, whilst unstable/non-STEMI patients are generally non-elective cases. Using this rule, we must exclude from the BCIS Audit 2006 totals the 11% of PCIs indicated for STEMI, and consider only the Stable Angina cases as elective. After recalculating proportions without STEMI cases, the balance between elective and non-elective admissions becomes 57.0% : 43.0%.

The BCIS consultation response also states that: "BCIS has always argued that a value of 13% for absolute risk is justified from the randomised trials and registries in the worldwide literature" and therefore argues that the Appraisal Committee preferred value of 11% at 12 months should be increased. In order to achieve this overall baseline risk rate at the same time as using the revised elective:non-elective balance and preserving the relative differences between types of presentation, it is necessary to employ new baseline risks of 11.5% for electives and 15.0% fot non-electives.

3.1.2 Subgroup risk of revascularisation and DES effectiveness

BCIS propose the use of repeat intervention relative risk multipliers for the three conventional risk factors (1.75 for small vessels, 1.35 for long lesions and 1.52 for

diabetes) based on an unweighted average of multipliers derived from a wide range of sources covering different outcome definitions over different time periods and with differently defined populations (BCIS Table 1). In addition, they prefer similarly derived estimates of the relative effectiveness of DES (0.69 for small vessels, 0.70 for long lesions, 0.61 for diabetes and 0.60 for the overall population) in reducing these risks (BCIS Table 2).

In order to employ these two sets of values in the model it is necessary to break the assumptions of statistical independence between these variables which allow the estimation of combined risk parameters for the full set of eight possible combinations of these three risks as shown in previous model results (this was possible because the size of the three relative risk parameters were jointly estimated from a single dataset, and so mutually compatible). Therefore in the following set of model results, which add BCIS risk and effectiveness values to the other changes used in Analysis 1, it is only possible to provide meaningful results for the overall combined population, and the three single-risk sub-groups.

3.2 Results

The results of Analysis 2 are shown in Table B, in the same format as used in earlier Addenda. In this case all the calculable ICERs are improved. This has only a marginal effect on the value of the price premium below which DES appear to be cost-effective (still between £200 and £300 per stent), but a larger effect on the three high risk sub-groups which appear to be cost-effective if the DES price premium is below £400-450 per stent.

Table B: Results of Analysis 2 incorporating alternative assumptions for baseline repeat intervention risk, sub-group relative risks, balance of elective and non-elective PCI cases, and relative effectiveness of DES in sub-groups, plus Analysis 1 changes

Combined Elective & Non-Elective Index PCI

1.551 stents per patient on average

Conventional risk factors			Absolute risk	Incremental utilty	Incremental cost by levels of price premium								Incremental cost per QALY by levels of price premium							
Long lesion	Small vessel	Diabetes			£100	£200	£300	£400	£500	£600	£700	£800	£100	£200	£300	£400	£500	£600	£700	£800
No	No	No	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Yes	No	No	17.6%	0.00895	-£260	-£116	£28	£171	£315	£459	£603	£747	-£29,000	-£13,000	£3,100	£19,100	£35,200	£51,300	£67,300	£83,400
No	No	Yes	19.8%	0.00879	-£249	-£106	£38	£182	£325	£469	£613	£757	-£28,400	-£12,000	£4,300	£20,700	£37,000	£53,300	£69,700	£86,000
No	Yes	No	22.8%	0.01129	-£358	-£155	£49	£253	£456	£660	£863	£1,067	-£31,700	-£13,700	£4,300	£22,400	£40,400	£58,500	£76,500	£94,500
Yes	No	Yes	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Yes	Yes	No	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
No	Yes	Yes	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Yes	Yes	Yes	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Overall			13.0%	0.00611	-£63	£86	£235	£383	£532	£681	£829	£978	-£10,300	£14,000	£38,400	£62,700	£87,000	£111,400	£135,700	£160,000

4. Conclusion

The criticisms and suggestions made by BCIS (and also quoted by several other consultees) have been addressed in this Addendum. Analysis 1 incorporates updated UK costs adjusted for consistency with other model assumptions, increased mean exposure time to anginal symptoms, and higher estimated underlying clopidogrel use. Additionally, Analysis 2 adjusts the elective : non-elective casemix on the basis of the latest BCIS audit, and tests the implications of a higher baseline risk of repeat revascularization, and BCIS preferred relative risks for conventional risk factors.

Results for Analysis 1 show only modest changes from previously reported results, with cost-effectiveness apparent only for some high risk groups for levels of the price premium below £300-400 per stent. Analysis 2 further improves the apparent cost-effectiveness of high risk groups suggesting that the price premium of £400-500 might be acceptable.

However, it is important to recognise that several important elements in these analyses remain controversial (especially, the mean time with anginal symptoms, the overall baseline risk and the relative risk multipliers for risk factors) and would be considered unduly generous by LRiG.

References

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